The American Journal of Cardiology

JANUARY 1, 1990

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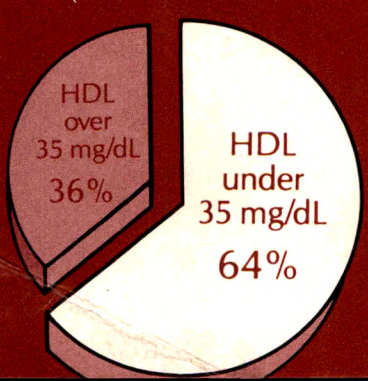
240 TOTAL

<35 HDL mg/dL

What's a common denominator of most heart attack victims?

Mixed hyperlipidemias—elevated cholesterol *and* triglycerides—are common among heart attack victims,[1] and nearly two-thirds of people who developed myocardial infarction in the PROCAM Trial had a low (<35 mg/dL) baseline level of HDL cholesterol.[2]

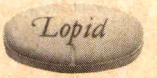
HEART ATTACK PATIENTS
(PROCAM TRIAL)[2]



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A powerful case for LOPID® (gemfibrozil)





BID 600-mg Tablets

Raised low HDL 25%

—in patients whose baseline HDL was below 35 mg/dL in the landmark Helsinki Heart Study (HHS).[3]

Reduced heart attack incidence* up to 62%

—in these HHS patients and 45% in HHS patients whose baseline HDL was below the median (46.4 mg/dL). Incidence of serious coronary events was similar for LOPID and placebo subgroups with baseline HDL above the median (46.4 mg/dL).[3]

Raised HDL levels 1½ to 3 times more effectively than lovastatin

—in a 12-week, double-blind, randomized trial among patients with moderate to severe hyperlipidemia. Lovastatin achieved greater reductions in total serum cholesterol than gemfibrozil in this study population.[4]

RAISES HDL DRAMATICALLY REDUCES HEART ATTACK

LOPID is indicated for reducing the risk of coronary heart disease (CHD) in Type IIb patients with low HDL, in addition to elevated LDL and triglycerides, and who have had an inadequate response to weight loss, diet, exercise, and other pharmacologic agents such as bile acid sequestrants and nicotinic acid.

*Defined as a combination of definite coronary death and/or definite myocardial infarction.

References: 1. Goldstein JL, Hazzard WR, Schrott HG, Bierman EL, Motulsky AG. Hyperlipidemia in coronary heart disease. I. Lipid levels in 500 survivors of myocardial infarction. *J Clin Invest.* 1973;52:1533-1543. **2.** Assmann G, Schulte H. *PROCAM-Trial: Prospective Cardiovascular Münster Trial.* Zürich: Panscientia Verlag; 1986:8-9. **3.** Data on file, Medical Affairs Dept, Parke-Davis **4.** Tikkanen MJ, Helve E, Jäättelä A, et al. Comparison between lovastatin and gemfibrozil in the treatment of primary hypercholesterolemia: the Finnish Multicenter Study. *Am J Cardiol.* 1988;62:35J-43J.

Please see last page of this advertisement for warnings, contraindications, and brief summary of prescribing information.

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Before prescribing, please see full prescribing information.
A Brief Summary follows.

CONTRAINDICATIONS. 1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.

2. Preexisting gallbladder disease (See WARNINGS).

3. Hypersensitivity to gemfibrozil.

WARNINGS. 1. Because of chemical, pha[redacted]gical, and clinical similarities between gemfibrozil and clofibrate, the a[redacted]s with clofibrate in two large clinical studies may also apply to gemfibrozi[redacted]ose studies, the Coronary Drug Project, 1000 subjects with previous m[redacted]tion were treated for five years with clofibrate. There was no difference[redacted]ween the clofibrate-treated subjects and 3000 placebo-treated subject[redacted]many clofibrate-treated subjects developed cholelithiasis and cholecysti[redacted]urgery. In the other study, conducted by the World Health Organizatio[redacted]HO), [redacted]00 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant, 29%, higher total mortality in the clofibrate-treated than in a comparable placebo-treated control group. The excess mortality was due to a 33% increase in noncardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

During the Helsinki Heart Study and in the 1½ year follow-up period since the trial was completed, mortality from any cause was 59 (2.9%) in the Lopid group and 55 (2.7%) in the placebo group. Mortality from any cause during the double-blind portion of the study was 44 deaths in the Lopid group and 43 in the placebo group. Because of the more limited size of the Helsinki Heart Study, this result is not statistically-significantly different from the 29% excess mortality seen in the clofibrate group in the separate WHO study. Noncoronary heart disease related mortality showed a 58% greater trend in the Lopid group (43 vs 27 patients in the placebo group, p=0.056).

In the Helsinki Heart Study, the incidence of total malignancies discovered during the trial and in the 1½ years since the trial was completed was 39 in the Lopid group and 29 in the placebo group (difference not statistically significant). This includes 5 basal cell carcinomas in the Lopid group and none in the placebo group (p=0.06; historical data predicted an expected 4.7 cases in the placebo group). GI malignancies and deaths from malignancies were not statistically different between Lopid and placebo subgroups. Follow-up of the Helsinki Heart Study participants will provide further information on cause-specific mortality and cancer morbidity.

2. A gallstone prevalence substudy of 450 Helsinki Heart Study participants showed a trend toward a greater prevalence of gallstones during the study within the Lopid treatment group (7.5% vs 4.9% for the placebo group, a 55% excess for the gemfibrozil group). A trend toward a greater incidence of gallbladder surgery was observed for the Lopid group (17 vs 11 subjects, a 54% excess). This result did not differ statistically from the increased incidence of cholecystectomy observed in the WHO study in the group treated with clofibrate. Both clofibrate and gemfibrozil may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Lopid therapy should be discontinued if gallstones are found.

3. Since a reduction of mortality from coronary artery disease has not been demonstrated and because liver and interstitial cell testicular tumors were increased in rats, Lopid should be administered only to those patients described in the INDICATIONS AND USAGE section. If a significant serum lipid response is not obtained, Lopid should be discontinued.

4. Concomitant Anticoagulants—Caution should be exercised when anticoagulants are given in conjunction with Lopid. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

5. Concomitant therapy with Lopid and Mevacor® (lovastatin) has been associated with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure (See Drug Interactions). The use of fibrates alone, including Lopid, may occasionally be associated with myositis. Patients receiving Lopid and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myositis, including serum creatine kinase level determination. If myositis is suspected or diagnosed, Lopid therapy should be withdrawn.

6. Cataracts—Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of male rats treated with gemfibrozil at 10 times the human dose.

PRECAUTIONS. 1. **Initial Therapy**—Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal. Before instituting Lopid therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities.

2. **Continued Therapy**—Periodic determination of serum lipids should be obtained, and the drug withdrawn if lipid response is inadequate after 3 months of therapy.

3. **Drug Interactions**—(A) **Lovastatin:** Rhabdomyolysis has occurred with combined gemfibrozil and lovastatin therapy. It may be seen as early as 3 weeks after initiation of combined therapy or after several months. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. There is no assurance that periodic monitoring of creatine kinase will prevent the occurrence of severe myopathy and kidney damage.

(B) **Anticoagulants:** CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

4. **Carcinogenesis, Mutagenesis, Impairment of Fertility**—Long-term studies have been conducted in rats and mice at one and ten times the human dose. The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant (p=0.1). In high dose female rats, there was a significant increase in the combined incidence of benign, and malignant liver neoplasms. In male and female mice, there were no statistically significant differences

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from controls in the incidence of liver tumors, but the doses tested were lower than those shown to be carcinogenic with other fibrates.

Male rats had a dose-related and statistically significant increase of benign Leydig cell tumors at 1 and 10 times the human dose.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following Lopid administration to the male rat. An adequate study to test for peroxisome proliferation has not been done in humans but changes in peroxisome morphology have been observed. Peroxisome proliferation has been shown to occur in humans with either of two other drugs of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Administration of approximately three or ten times the human dose to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to the offspring.

5. **Pregnancy Category B**—Reproduction studies have been performed in the rat at doses 3 and 9 times the human dose, and in the rabbit at 2 and 6.7 times the human dose. These studies have revealed no evidence of impaired fertility in females or harm to the fetus due to Lopid. Minor fetotoxicity was manifested by reduced birth rates observed at the high dose levels. No significant malformations were found among almost 400 offspring from 36 litters of rats and 100 fetuses from 22 litters of rabbits.

There are no studies in pregnant women. In view of the fact that Lopid is tumorigenic in male and female rats, the use of Lopid in pregnancy should be reserved for those patients where the benefit clearly outweighs the possible risk to the patient or fetus.

6. **Nursing Mothers**—Because of the potential for tumorigenicity shown for gemfibrozil in rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

7. **Hematologic Changes**—Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of Lopid therapy. However, these levels stabilize during long-term administration. Rarely, severe anemia, leukopenia, thrombocytopenia, and bone marrow hypoplasia have been reported. Therefore, periodic blood counts are recommended during the first 12 months of Lopid administration.

8. **Liver Function**—Abnormal liver function tests have been observed occasionally during Lopid administration, including elevations of AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase. These are usually reversible when Lopid is discontinued. Therefore periodic liver function studies are recommended and Lopid therapy should be terminated if abnormalities persist.

9. **Use in Children**—Safety and efficacy in children have not been established.

ADVERSE REACTIONS. In the double-blind controlled phase of the Helsinki Heart Study, 2046 patients received Lopid for up to 5 years. In that study, the following adverse reactions were statistically more frequent in subjects in the Lopid group (placebo incidence in parentheses): gastrointestinal reactions, 34.2% (23.8%); dyspepsia, 19.6% (11.9%); abdominal pain, 9.8% (5.6%); acute appendicitis (histologically confirmed in most cases where data are available), 1.2% (0.6%); atrial fibrillation, 0.7% (0.1%).

Adverse events reported by more than 1% of subjects, but without a significant difference between groups (placebo incidence in parentheses) were: diarrhea, 7.2% (6.5%); fatigue, 3.8% (3.5%); nausea/vomiting, 2.5% (2.1%); eczema, 1.9% (1.2%); rash, 1.7% (1.3%); vertigo, 1.5% (1.3%); constipation, 1.4% (1.3%); headache, 1.2% (1.1%).

Gallbladder surgery was performed in 0.9% of Lopid and 0.5% of placebo subjects, a 64% excess, which is not statistically different from the excess of gallbladder surgery observed in the clofibrate compared to the placebo group of the WHO study.

Nervous system and special senses adverse reactions were more common in the Lopid group. These included hypesthesia, paresthesias, and taste perversion. Other adverse reactions that were more common among Lopid treatment group subjects but where a causal relationship was not established include cataracts, peripheral vascular disease, and intracerebral hemorrhage.

From other studies it seems probable that Lopid is causally related to the occurrence of **musculoskeletal symptoms** (See WARNINGS), and to **abnormal liver function tests** and **hematologic changes** (See PRECAUTIONS).

Reports of viral and bacterial infections (common cold, cough, urinary tract infections) were more common in gemfibrozil-treated patients in other controlled clinical trials of 805 patients.

Additional adverse reactions that have been reported for gemfibrozil are listed below by system. These are categorized according to whether a causal relationship to treatment with Lopid is probable or not established:

CAUSAL RELATIONSHIP PROBABLE: *Gastrointestinal:* cholestatic jaundice; *Central Nervous System:* dizziness, somnolence, paresthesia, peripheral neuritis, decreased libido, depression, headache; *Eye:* blurred vision; *Genitourinary:* impotence; *Musculoskeletal:* myopathy, myasthenia, myalgia, painful extremities, arthralgia, synovitis, rhabdomyolysis (see WARNINGS and Drug Interactions under PRECAUTIONS); *Clinical Laboratory:* increased creatine phosphokinase, increased bilirubin, increased liver transaminases (AST [SGOT], ALT [SGPT]), increased alkaline phosphatase; *Hematopoietic:* anemia, leukopenia, bone marrow hypoplasia, eosinophilia; *Immunologic:* angioedema, laryngeal edema, urticaria; *Integumentary:* exfoliative dermatitis, rash, dermatitis, pruritus.

CAUSAL RELATIONSHIP NOT ESTABLISHED: *General:* weight loss; *Cardiac:* extrasystoles; *Gastrointestinal:* pancreatitis, hepatoma, colitis; *Central Nervous System:* confusion, convulsions, syncope; *Eye:* retinal edema; *Genitourinary:* decreased male fertility; *Clinical Laboratory:* positive antinuclear antibody; *Hematopoietic:* thrombocytopenia; *Immunologic:* anaphylaxis, Lupus-like syndrome, vasculitis; *Integumentary:* alopecia.

DOSAGE AND ADMINISTRATION. The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal.

MANAGEMENT OF OVERDOSE. While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

References: 1. Frick MH, Elo O, Haapa K, et al: Helsinki Heart Study: Primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia. *N Engl J Med* 1987;317:1237-1245. 2. Manninen V, Elo O, Frick MH, et al: Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study. *JAMA* 1988; 260:641-651. 3. Nikkila EA: Familial lipoprotein lipase deficiency and related disorders of chylomicron metabolism. In Stanbury J. B. et al. (eds.): *The Metabolic Basis of Inherited Disease,* 5th ed., McGraw-Hill, 1983, Chap. 30, pp. 622-642.

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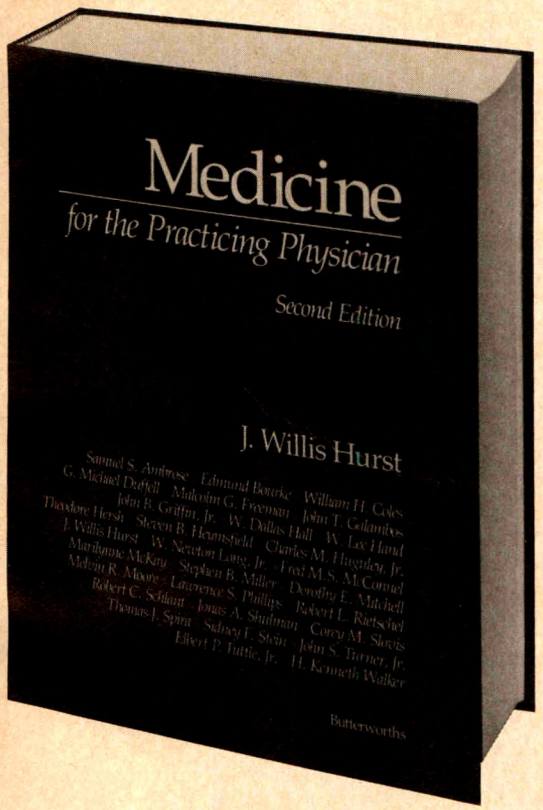
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THE AMERICAN JOURNAL OF CARDIOLOGY.® (ISSN 0002-9149) January 1, 1990, Vol. 65, No. 1 (USPS: 505-750).
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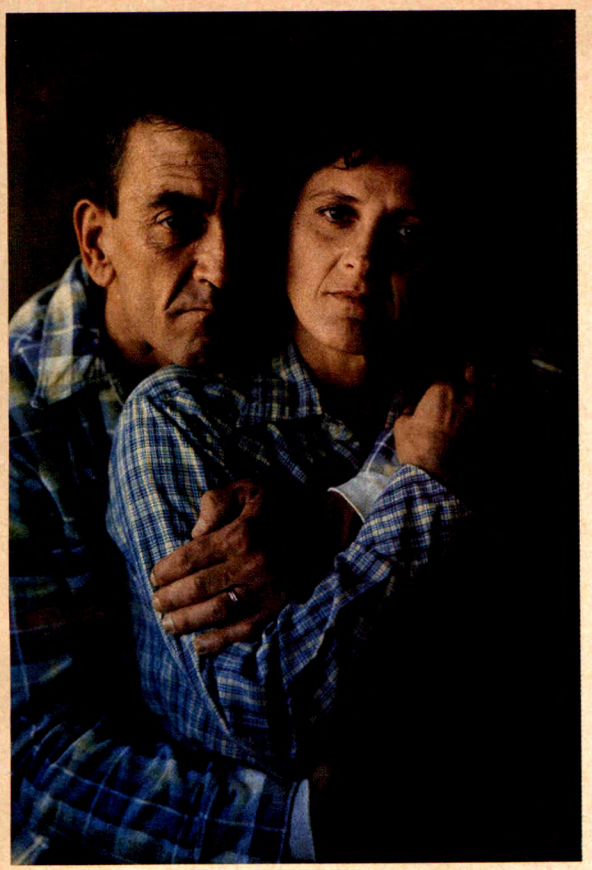
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Consult full prescribing information before using.

INDICATIONS AND USAGE: ACTIVASE® is indicated for use in the management of acute myocardial infarction (AMI) in adults for the lysis of thrombi obstructing coronary arteries, the reduction of infarct size, the improvement of ventricular function following AMI, the reduction of the incidence of congestive heart failure and the reduction of mortality associated with AMI. Treatment should be initiated as soon as possible after the onset of AMI symptoms.

CONTRAINDICATIONS: Because thrombolytic therapy increases the risk of bleeding, ACTIVASE® is contraindicated in the following situations: • Active internal bleeding • History of cerebrovascular accident • Recent (within two months) intracranial or intraspinal surgery or trauma (see WARNINGS) • Intracranial neoplasm, arteriovenous malformation, or aneurysm • Known bleeding diathesis • Severe uncontrolled hypertension.

WARNINGS: Bleeding The most common complication encountered during ACTIVASE® therapy is bleeding. The type of bleeding associated with thrombolytic therapy can be divided into two broad categories: • Internal bleeding involving the gastrointestinal or genitourinary tract, or retroperitoneal or intracranial sites • Superficial or surface bleeding, observed mainly at invaded or disturbed sites (e.g., sites of venous cutdown, arterial puncture, recent surgical intervention).

Concomitant use of heparin anticoagulation may contribute to bleeding. Some hemorrhagic episodes occurred one or more days after the effects of ACTIVASE® had dissipated, but while heparin therapy was continuing.

As fibrin is lysed during ACTIVASE® therapy, bleeding from recent puncture sites may occur. Therefore, thrombolytic therapy requires careful attention to all potential bleeding sites (including sites of catheter insertion, arterial and venous puncture, cutdown and needle puncture).

Intramuscular injections and nonessential handling of the patient should be avoided during treatment with ACTIVASE® Venipunctures should be performed carefully and only as required.

Should an arterial puncture be necessary during an infusion of ACTIVASE® it is preferable to use an upper extremity vessel accessible to manual compression. Pressure should be applied for at least 30 minutes, a pressure dressing applied and the puncture site checked frequently for evidence of bleeding.

Should serious bleeding (not controllable by local pressure) occur, the infusion of ACTIVASE® and any concomitant heparin should be terminated immediately.

Each patient being considered for therapy with ACTIVASE® should be carefully evaluated and anticipated benefits weighed against potential risks associated with therapy.

In the following conditions, the risks of ACTIVASE® therapy may be increased and should be weighed against the anticipated benefits: • Recent (within 10 days) major surgery, obstetrical delivery, organ biopsy, previous puncture of noncompressible vessels • Cerebrovascular disease • Recent (within 10 days) gastrointestinal or genitourinary bleeding • Recent (within 10 days) trauma • Hypertension: systolic BP≥180 mm Hg and/or diastolic BP≥110 mm Hg • High likelihood of left heart thrombus, e.g., mitral stenosis with atrial fibrillation • Acute pericarditis • Subacute bacterial endocarditis • Hemostatic defects including those secondary to severe hepatic or renal disease • Significant liver dysfunction • Pregnancy • Diabetic hemorrhagic retinopathy, or other hemorrhagic ophthalmic conditions • Septic thrombophlebitis or occluded AV cannula at seriously infected site • Advanced age, i.e., over 75 years old • Patients currently receiving oral anticoagulants • Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location.

Arrhythmias Coronary thrombolysis may result in arrhythmias associated with reperfusion. These arrhythmias are not different from those often seen in the ordinary course of AMI and may be managed with standard antiarrhythmic measures. It is recommended that antiarrhythmic therapy for bradycardia and/or ventricular irritability be available when infusions of ACTIVASE® are administered.

PRECAUTIONS: General Standard management of MI should be implemented concomitantly with ACTIVASE® treatment. Noncompressible arterial puncture must be avoided. Arterial and venous punctures should be minimized. In the event of serious bleeding, ACTIVASE® and heparin should be discontinued immediately. Heparin effects can be reversed by protamine.

Readministration There is no experience with readministration of ACTIVASE® If anaphylactoid reaction occurs, infusion should be discontinued immediately and appropriate therapy initiated.

Although sustained antibody formation in patients receiving one dose of ACTIVASE® has not been documented, readministration should be undertaken with caution.

Laboratory Tests During ACTIVASE® therapy, results of coagulation tests and/or measures of fibrinolytic activity may be unreliable unless specific precautions are taken to prevent *in vitro* artifacts. ACTIVASE® is an enzyme that when present in blood in pharmacologic concentrations remains active under *in vitro* conditions. This can lead to degradation of fibrinogen in blood samples removed for analysis. Collection of blood samples in the presence of aprotinin (150-200 units/mL) can to some extent mitigate this phenomenon.

Drug Interactions The interaction of ACTIVASE® with other cardioactive drugs has not been studied. In addition to bleeding associated with heparin and vitamin K antagonists, drugs that alter platelet function may increase the risk of bleeding if administered prior to, during or after ACTIVASE® therapy.

Use of Anticoagulants Heparin has been administered concomitantly with and following infusions of ACTIVASE® to reduce the risk of rethrombosis. Because either heparin or ACTIVASE® alone may cause bleeding complications, careful monitoring for bleeding is advised, especially at arterial puncture sites.

Pregnancy (Category C) Animal reproduction studies have not been conducted with ACTIVASE®. It is also not known whether ACTIVASE® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ACTIVASE® should be given to a pregnant woman only if clearly needed.

Pediatric Use Safety and effectiveness of ACTIVASE® in children has not been established.

Carcinogenesis, Mutagenesis, Impairment of Fertility Long-term studies in animals have not been performed to evaluate the carcinogenic potential or the effect on fertility. Short-term studies, which evaluated tumorigenicity of ACTIVASE® and effect on tumor metastases in rodents, were negative.

Studies to determine mutagenicity (Ames test) and chromosomal aberration assays in human lymphocytes were negative at all concentrations tested. Cytotoxicity, as reflected by a decrease in mitotic index, was evidenced only after prolonged exposure and only at the highest concentrations tested.

Nursing Mothers It is not known whether ACTIVASE® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ACTIVASE® is administered to a nursing woman.

ADVERSE REACTIONS: Bleeding The most frequent adverse reaction associated with ACTIVASE® is bleeding. The type of bleeding associated with thrombolytic therapy can be divided into two broad categories: • Internal bleeding involving the gastrointestinal or genitourinary tract, or retroperitoneal or intracranial sites • Superficial or surface bleeding, observed mainly at invaded or disturbed sites (e.g., sites of venous cutdown, arterial puncture, recent surgical intervention).

The following incidence of significant internal bleeding (estimated as >250 cc blood loss) has been reported in studies in over 800 patients treated at all doses:

	Total Dose ≤ 100 mg	Total Dose > 100 mg
gastrointestinal	5%	5%
genitourinary	4%	4%
ecchymosis	1%	<1%
retroperitoneal	<1%	<1%
epistaxis	<1%	<1%
gingival	<1%	<1%

The incidence of intracranial bleeding in patients treated with ACTIVASE®, Alteplase, recombinant, is as follows:

Dose	Number of Patients	%
100 mg	3272	0.4
150 mg	1779	1.3
1-1.4 mg/kg	237	0.4

These data indicate that a dose of 150 mg of ACTIVASE® should not be used because it has been associated with an increase in intracranial bleeding.

Recent data indicate that the incidence of stroke in 6 randomized double-blind placebo controlled trials[1-7] is not signficantly different in the ACTIVASE® treated patients compared to those treated with placebo (37/3161, 1.2% versus 27/3092, 0.9%, respectively) ($p = 0.26$).

Should serious bleeding in a critical location (intracranial, gastrointestinal, retroperitoneal, pericardial) occur, ACTIVASE® therapy should be discontinued immediately, along with any concomitant therapy with heparin.

Fibrin, which is part of the hemostatic plug formed at needle puncture sites, will be lysed during ACTIVASE® therapy. Therefore, ACTIVASE® therapy requires careful attention to potential bleeding sites.

Allergic Reactions No serious or life-threatening allergic reactions have been reported. Other mild hypersensitivity reactions such as urticaria have been observed occasionally.

Other Adverse Reactions Other adverse reactions have been reported, principally nausea and/or vomiting, hypotension, and fever. These reactions are frequent sequelae of MI and may or may not be attributable to ACTIVASE® therapy.

DOSAGE AND ADMINISTRATION: Administer ACTIVASE® as soon as possible after the onset of symptoms.

ACTIVASE® is for intravenous administration only.

The recommended dose is 100 mg administered as 60 mg (34.8 million IU) in the first hour (of which 6 to 10 mg is administered as a bolus over the first 1-2 minutes), 20 mg (11.6 million IU) over the second hour, and 20 mg (11.6 million IU) over the third hour. For smaller patients (less than 65 kg), a dose of 1.25 mg/kg administered over 3 hours, as described above, may be used.[8]

A DOSE OF 150 MG OF ACTIVASE® SHOULD NOT BE USED BECAUSE IT HAS BEEN ASSOCIATED WITH AN INCREASE IN INTRACRANIAL BLEEDING.

Although the use of anticoagulants and antiplatelet drugs during and following administration of ACTIVASE® has not been shown to be of unequivocal benefit, heparin has been administered concomitantly for 24 hours or longer in more than 90% of patients. Aspirin and/or dipyridamole have been given either during and/or following heparin treatment.

Reconstitution and Dilution DO NOT USE IF VACUUM IS NOT PRESENT.

ACTIVASE® should be reconstituted by aseptically adding the appropriate volume of the accompanying Sterile Water for Injection, USP to the vial. It is important that ACTIVASE® be reconstituted only with Sterile Water for Injection, USP, without preservatives. Do not use Bacteriostatic Water for Injection, USP. The reconstituted preparation results in a colorless to pale yellow transparent solution containing ACTIVASE® 1.0 mg/mL at approximately pH 7.3. The osmolality of this solution is approximately 215 mOsm/kg.

Because ACTIVASE® contains no antibacterial preservatives, it should be reconstituted immediately before use. The solution may be used for intravenous administration within 8 hours following reconstitution when stored between 2-30°C. Before further dilution or administration, the product should be visually inspected for particulate matter and discoloration prior to administration whenever solution and container permit.

ACTIVASE® is stable for up to 8 hours in these solutions at room temperature. Exposure to light has no effect on the stability of these solutions. Excessive agitation during dilution should be avoided; mixing should be accomplished with gentle swirling and/or slow inversion. Do not use other infusion solutions, e.g., Sterile Water for Injection, USP or preservative-containing solutions for further dilution.

No other medication should be added to infusion solutions containing ACTIVASE®. Any unused infusion solution should be discarded.

HOW SUPPLIED: ACTIVASE® is supplied as a sterile, lyophilized powder in 20 mg and 50 mg vials containing vacuum, each packaged with diluent for reconstitution.

Storage Store lyophilized ACTIVASE® at controlled room temperature not to exceed 30°C (86°F), or under refrigeration (2-8°C/36-46°F). Protect the lyophilized material during extended storage from excessive exposure to light.

Do not use beyond the expiration date stamped on the vial.

ACTIVASE®, Alteplase, recombinant
Manufactured by
GENENTECH®, INC.
460 Point San Bruno Blvd.
South San Francisco, CA 94080
April, 1989

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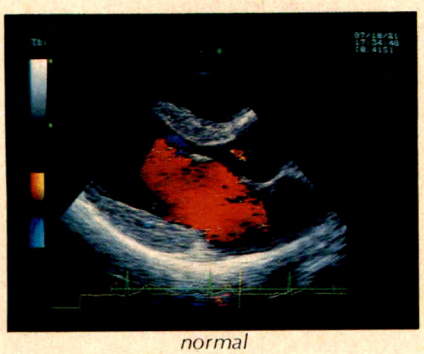
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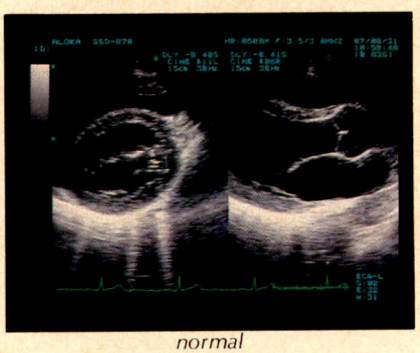


CATCH EVERY MOVE THEY MAKE ALOKA SSD-870 COLOR DOPPLER

Real-time two-dimensional ultrasound system for blood flow imaging with Cine Memory.



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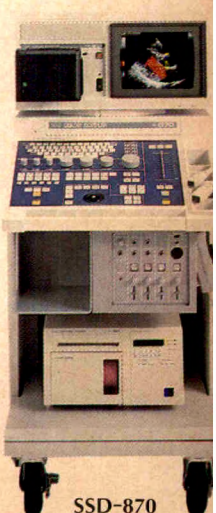


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Then at your convenience, the study can be analyzed frame by frame to aid your diagnosis. Aloka's development of high performance imaging technology allows the dual 32-frame Cine Memory to display images with 60-frame-per-second accuracy. And multi-functional phased array transducers have been developed for the Aloka SSD-870.

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SSD-870

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ALOKA

ALOKA CO.,LTD.: 6-22-1 Mure, Mitaka-shi, Tokyo 181, Japan
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Michael Miller, Lucy A. Mead, Peter O. Kwiterovich, Jr., and Thomas A. Pearson

To examine dyslipidemias in a population with desirable cholesterol levels, we evaluated 1,000 patients undergoing diagnostic coronary arteriography. Our results (of 288 patients with desirable cholesterol levels, approximately 67% of men with angiographically demonstrated coronary artery disease and 80% of women with CAD had low levels of high density lipoprotein cholesterol) suggest that all CAD patients should be screened for dyslipidemias, regardless of the plasma (or serum) total cholesterol level.

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Blood Cholesterol Screening in Several Environments Using a Portable, Dry-Chemistry Analyzer and Fingerstick Blood Samples
Reagan H. Bradford, Paul S. Bachorik, Karen Roberts, O. Dale Williams, and Antonio M. Gotto, Jr., for the Lipid Research Clinics Cholesterol Screening Study Group

Cholesterol was measured with a portable, dry-chemistry analyzer using capillary blood obtained by fingerstick in a total of 13,824 participants in a multicenter study of blood cholesterol screening performed in several medical and nonmedical environments. The new technology for blood cholesterol measurement we evaluated has proven to be a feasible and reliable means for measuring blood cholesterol in typical screening settings.

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Harold L. Kennedy, Sondra M. Seiler, Michael K. Sprague, Sharon M. Homan, James A. Whitlock, Morton J. Kern, Michel G. Vandormael, Hendrick B. Barner, John E. Codd, and Vallee L. Willman, with the technical assistance of Debra Lyyski

We prospectively assessed the prevalence and characteristics of silent myocardial ischemia as detected by 24-hour ambulatory electrocardiographic ST-segment depression in 94 patients examined early and 184 patients examined late after coronary artery bypass grafting, and followed for a mean of 48 ± 11 months. Our data show that ambulatory ECG silent ischemia detected during the first year after CABG in patients with predominantly good left ventricular function is not associated with an adverse prognosis.

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Frequency and Significance of Late Evolution of Q Waves in Patients with Initial Non-Q-Wave Acute Myocardial Infarction
Robert E. Kleiger, William E. Boden, Kenneth B. Schechtman, Robert S. Gibson, David J. Schwartz, Barbara J. Geiger, Robert J. Capone, Robert Roberts, and the Diltiazem Reinfarction Study Group

Serial 12-lead electrocardiograms and plasma creatine kinase-MB values from 544 patients with confirmed non-Q-wave acute myocardial infarction were analyzed to define the rate of progression of non-Q-wave AMI to Q-wave AMI and to examine its relation to CK-MB evidence of extension. This progression appears to involve 2 different mechanisms: temporal lag in the electrocardiogram, and actual extension by quantitative CK-MB criteria.

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James R. Bengtson, Daniel B. Mark, Michael B. Honan, David S. Rendall, Tomoaki Hinohara, Richard S. Stack, Mark A. Hlatky, Robert M. Califf, Kerry L. Lee, and David B. Pryor

What is the value of a 6-month exercise treadmill test for detecting restenosis after elective percutaneous transluminal coronary angioplasty? We studied 308 consecutive successful PTCA patients without a recent myocardial infarction; our results suggest that for more accurate detection of restenosis, the exercise treadmill test must be supplemented by a more definitive test.

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H. Vernon Anderson, J. David Talley, Alexander J.R. Black, Gary S. Roubin, John S. Douglas, and Spencer B. King, III

What is the optimal therapy for patients with asymptomatic coronary artery disease? Coronary angioplasty performed in 114 asymptomatic patients, most with exercise-induced silent myocardial ischemia, achieved very good primary success and was accompanied by low cardiac event rates and no deaths over several years of patient follow-up.

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Joel Morganroth, J. Thomas Bigger, Jr., and Jeffrey L. Anderson

To define the practice habits of United States cardiologists in the treatment of ventricular arrhythmias, we sent a random sample of 1,000 of 12,000 cardiologists a pretested questionnaire; 252 responded. Significant lack of consensus exists on the toxicity of antiarrhythmic drugs, use of electrophysiologic testing and in- versus out-of-hospital drug initiation.

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Effect of Basic Drive Cycle Length on the Yield of Ventricular Tachycardia During Programmed Ventricular Stimulation

Joni Summitt, Shimon Rosenheck, William H. Kou, Stephen Schmaltz, Alan H. Kadish, and Fred Morady

In patients in whom sustained, monomorphic ventricular tachycardia was inducible by programmed stimulation with 1 to 3 ventricular extrastimuli at the right ventricular apex, the yield of VT was 88% when a drive cycle length of 400 ms was used, compared to 64% when the drive cycle length was 600 ms and 32% when the extrastimuli were introduced during sinus rhythm. These results suggest that it is more efficient to begin programmed stimulation using a basic drive cycle length of 400 ms instead of 600 ms or sinus rhythm.

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New Insights into Pacemaker Syndrome Gained from Hemodynamic, Humoral and Vascular Responses During Ventriculo-Atrial Pacing

Kenneth A. Ellenbogen, Marc D. Thames, and Pramod K. Mohanty

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Assessment of Four Ambulatory Blood Pressure Monitors and Measurements by Clinicians Versus Intraarterial Blood Pressure at Rest and During Exercise

William B. White, Per Lund-Johansen, and Per Omvik

We assessed the accuracy of 4 different ambulatory blood pressure monitors by comparing them to simultaneous intraarterial BP (contralateral brachial artery) during rest, isometric and dynamic (bicycle) exercise in 48 hypertensive patients undergoing invasive hemodynamic evaluation. Our data show that at rest, noninvasive ambulatory BP monitors are similar in accuracy to that of clinicians in BP determination but during exercise there are differences among the monitors that make some of them unsuitable for measurements while in motion.

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David S. Berger and John K.-J. Li

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Failure of Balloon Aortic Valvuloplasty to Result in Sustained Clinical Improvement in Patients with Depressed Left Ventricular Function

Charles J. Davidson, J. Kevin Harrison, Mark E. Leithe, Katherine B. Kisslo, and Thomas M. Bashore

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Michael G. Spain, Mikel D. Smith, Oi Ling Kwan, and Anthony N. DeMaria

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Junichiro Hayano, Masami Yamada, Yusaku Sakakibara, Takao Fujinami, Kiyoko Yokoyama, Yosaku Watanabe, and Kazuyuki Takata

To investigate the short- and long-term effects of cigarette smoking on autonomic cardiac regulation, we analyzed the changes in the heart rate spectral components with smoking and the differences in the components between nonsmokers and smokers after an overnight abstinence. Our results suggest that smoking causes not only short- but also long-term reduction in vagal cardiac control.

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Pressor Effect of Inhaled Ergotamine in Orthostatic Hypotension

Italo Biaggioni, Deborah Zygmunt, Virginia Haile, and David Robertson

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Aerobic Exercise Reduces Levels of Cardiovascular and Sympathoadrenal Responses to Mental Stress in Subjects Without Prior Evidence of Myocardial Ischemia
James A. Blumenthal, Mats Fredrikson, Cynthia M. Kuhn, Ross L. Ulmer, Margaret Walsh-Riddle, and Mark Appelbaum

Thirty-seven healthy type A men (mean age 42 years) were randomly assigned to either an aerobic exercise training group or to a strength and flexibility training group. Subjects underwent testing, including graded exercise treadmill testing and measurement of cardiovascular and neuroendocrine responses to mental arithmetic, before and at the completion of the exercise program. Our findings suggest that aerobic exercise reduces levels of cardiovascular and sympathoadrenal responses during and after mental stress.

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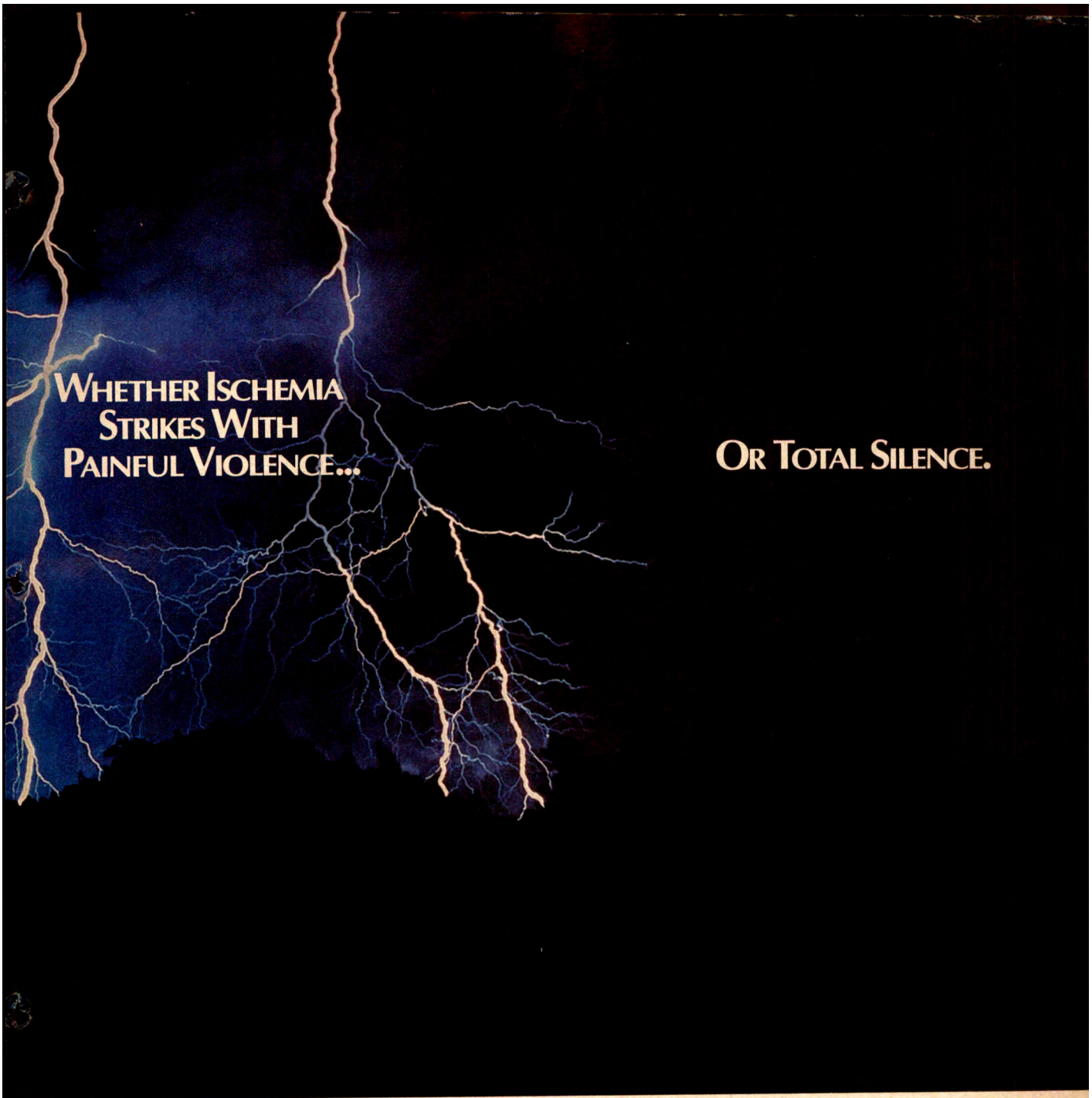
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TENORMIN reduces more than just *painful* myocardial ischemia. It reduces *painless* ischemia as well. Alone or in combination regimens, it lowers the total ischemic burden* and reduces the need for PRN nitroglycerin.[1-3]

*The sum of painful and painless episodes.

In Angina

ONE TABLET A DAY

TENORMIN® (atenolol)

PROTECTS THE HEART.



See adjacent page for brief summary of prescribing information.

ONE TABLET A DAY

TENORMIN® (atenolol)



PROTECTS THE HEART FROM PAINFUL AND PAINLESS ISCHEMIA.

A $beta_1$-selective (cardioselective) blocking agent.

DESCRIPTION: TENORMIN (atenolol), a synthetic, $beta_1$-selective (cardioselective) adrenoreceptor blocking agent, may be chemically described as benzeneacetamide, 4-[2'-hydroxy-3'-[(1-methylethyl) amino] propoxy]-. Atenolol (free base) has a molecular weight of 266. It is a relatively polar hydrophilic compound with a water solubility of 26.5 mg/mL at 37°C and a log partition coefficient (octanol/water) of 0.23. It is freely soluble in 1N HCl (300 mg/mL at 25° C) and less soluble in chloroform (3 mg/mL at 25°C).

TENORMIN is available as 50 mg and 100 mg tablets for oral administration.

Inactive ingredients: magnesium stearate, microcrystalline cellulose, povidone, sodium starch glycolate.

INDICATIONS AND USAGE: Hypertension: TENORMIN is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-type diuretic.

Angina Pectoris Due to Coronary Atherosclerosis: TENORMIN is indicated for the long-term management of patients with angina pectoris.

CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure. (See WARNINGS.)

WARNINGS: Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, TENORMIN should be administered cautiously. Both digitalis and atenolol slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic and the response observed closely. If cardiac failure continues despite adequate digitalization and diuresis, TENORMIN should be withdrawn. (See Dosage and Administration.)

Cessation of Therapy With TENORMIN: Patients with coronary artery disease, who are being treated with TENORMIN, should be advised against abrupt discontinuation of therapy. Severe exacerbation of angina and the occurrence of myocardial infarction and ventricular arrhythmias have been reported in angina patients following the abrupt discontinuation of therapy with other beta blockers. The last two complications may occur with or without preceding exacerbation of the angina pectoris. To date, there has been no report of myocardial infarction or severe angina upon withdrawal of TENORMIN, probably due to its long plasma half-life. Because of the problems encountered with other beta blockers, when discontinuation of TENORMIN is planned, the patients should be carefully observed and advised to limit physical activity to a minimum. If the angina worsens or acute coronary insufficiency develops, it is recommended that TENORMIN be promptly reinstituted, at least temporarily. (See Dosage and Administration.)

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative $beta_1$ selectivity, however, TENORMIN may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since $beta_1$ selectivity is not absolute, the lowest possible dose of TENORMIN should be used with therapy initiated at 50 mg, and a $beta_2$-stimulating agent (bronchodilator) should be made available. If dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels.

Anesthesia and Major Surgery: As with all beta-receptor blocking drugs it may be decided to withdraw TENORMIN before surgery. In this case, 48 hours should be allowed to elapse between the last dose and anesthesia. If treatment is continued, care should be taken when using anesthetic agents which depress the myocardium such as ether, cyclopropane, and trichloroethylene.

TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents (eg, dobutamine or isoproterenol with caution—see section on Overdosage). Manifestations of excessive vagal tone (eg, profound bradycardia, hypotension) may be corrected with atropine (1-2 mg IV).

Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm; therefore, patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely. (See Dosage and Administration.)

PRECAUTIONS: Impaired Renal Function: The drug should be used with caution in patients with impaired renal function. (See Dosage and Administration.)

Drug Interactions: Catecholamine-depleting drugs (eg, reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with TENORMIN plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Should it be decided to discontinue therapy in patients receiving beta blockers and clonidine concurrently, the beta blocker should be discontinued several days before the gradual withdrawal of clonidine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human dose, did not indicate a carcinogenic potential in rodents. Results of various mutagenicity studies support this finding.

Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose) was unaffected by atenolol administration.

Animal Toxicology: Chronic studies performed in animals have revealed the occurrence of vacuolation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels of atenolol (starting at 15 mg/kg/day or 7.5 times the maximum recommended human dose), and increased incidence of atrial degeneration of hearts of male rats at 300 mg but not 150 mg atenolol/kg/day (150 and 75 times the maximum recommended human dose, respectively).

USAGE IN PREGNANCY: Pregnancy Category C. Atenolol has been shown to produce a dose-related increase in embryo/fetal resorptions in rats at doses equal to or greater than 50 mg/kg/day or 25 or more times the maximum recommended human dose. Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg/day or 12.5 times the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. TENORMIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Atenolol is excreted in human breast milk at a ratio of 1.5 to 6.8 when compared to the concentration in plasma. Caution should be exercised when TENORMIN is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient. Frequency estimates were derived from controlled studies in which adverse reactions were either volunteered by the patient (US studies) or elicited, eg, by checklist (foreign studies). The reported frequency of elicited adverse effects was higher for both TENORMIN (atenolol) and placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects for TENORMIN and placebo is similar, causal relationship to TENORMIN is uncertain.

The following adverse-reaction data present frequency estimates in terms of percentages: first from the US studies (volunteered side effects) and then from both US and foreign studies (volunteered and elicited side effects):

US STUDIES (% ATENOLOL-% PLACEBO):

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (0%-0.5%), postural hypotension (2%-1%), leg pain (0%-0.5%)

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (4%-1%), vertigo (2%-0.5%), lightheadedness (1%-0%), tiredness (0.6%-0.5%), fatigue (3%-1%), lethargy (1%-0%), drowsiness (0.6%-0%), depression (0.6%-0.5%), dreaming (0%-0%)

GASTROINTESTINAL: diarrhea (2%-0%), nausea (4%-1%)

RESPIRATORY (see WARNINGS): wheeziness (0%-0%), dyspnea (0.6%-1%)

TOTALS US AND FOREIGN STUDIES:

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (12%-5%), postural hypotension (4%-5%), leg pain (3%-1%)

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (13%-6%), vertigo (2%-0.2%), lightheadedness (3%-0.7%), tiredness (26%-13%), fatigue (6%-5%), lethargy (3%-0.7%), drowsiness (2%-0.5%), depression (12%-9%), dreaming (3%-1%)

GASTROINTESTINAL: diarrhea (3%-2%), nausea (3%-1%)

RESPIRATORY (see WARNINGS): wheeziness (3%-3%), dyspnea (6%-4%)

MISCELLANEOUS: There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and, in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy.

POTENTIAL ADVERSE EFFECTS: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects of TENORMIN.

HEMATOLOGIC: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

ALLERGIC: Fever, combined with aching and sore throat, laryngospasm, and respiratory distress.

CENTRAL NERVOUS SYSTEM: Reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation of time and place, short-term memory loss, emotional lability with slightly clouded sensorium, decreased performance on neuropsychometrics.

GASTROINTESTINAL: Mesenteric arterial thrombosis, ischemic colitis.

OTHER: Reversible alopecia, Peyronie's disease, erythematous rash, Raynaud's phenomenon.

MISCELLANEOUS: The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with TENORMIN during investigational use and foreign marketing experience. Furthermore, a number of patients who had previously demonstrated established practolol reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the reaction.

OVERDOSAGE: To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. The most common effects expected with overdosage of a beta-adrenergic blocking agent are bradycardia, congestive heart failure, hypotension, bronchospasm, and hypoglycemia.

In the case of overdosage, treatment with TENORMIN should be stopped and the patient carefully observed. TENORMIN can be removed from the general circulation by hemodialysis. In addition to gastric lavage, the following therapeutic measures are suggested if warranted:

BRADYCARDIA: Atropine or another anticholinergic drug.

HEART BLOCK (SECOND OR THIRD DEGREE): Isoproterenol or transvenous cardiac pacemaker.

CONGESTIVE HEART FAILURE: Conventional therapy.

HYPOTENSION (DEPENDING ON ASSOCIATED FACTORS): Epinephrine rather than isoproterenol or norepinephrine may be useful in addition to atropine and digitalis.

BRONCHOSPASM: Aminophylline, isoproterenol, or atropine.

HYPOGLYCEMIA: Intravenous glucose.

DOSAGE AND ADMINISTRATION: Hypertension: The initial dose of TENORMIN is 50 mg given as one tablet a day either alone or added to diuretic therapy. The full effect of this dose will usually be seen within 1 to 2 weeks. If an optimal response is not achieved, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Increasing the dosage beyond 100 mg a day is unlikely to produce any further benefit.

TENORMIN may be used alone or concomitantly with other antihypertensive agents including thiazide-type diuretics, hydralazine, prazosin, and alpha-methyldopa.

Angina Pectoris: The initial dose of TENORMIN is 50 mg given as one tablet a day. If an optimal response is not achieved within 1 week, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Some patients may require a dosage of 200 mg once a day for optimal effect.

Twenty-four-hour control with once-daily dosing is achieved by giving doses larger than necessary to achieve an immediate maximum effect. The maximum early effect on exercise tolerance occurs with doses of 50 to 100 mg, but at these doses the effect at 24 hours is attenuated, averaging about 50% to 75% of that observed with once-a-day oral doses of 200 mg.

Patients with Renal Impairment: Since TENORMIN is excreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of TENORMIN occurs until creatinine clearance falls below 35 mL/min/1.73 m^2 (normal range is 100-150 mL/min/1.73 m^2); therefore, the following maximum dosages are recommended for patients with renal impairment:

Creatinine Clearance (mL/min/1.73 m^2)	Atenolol Elimination Half-life (h)	Maximum Dosage
15-35	16-27	50 mg daily
<15	>27	50 mg every other day

Patients on hemodialysis should be given 50 mg after each dialysis; this should be done under hospital supervision as marked falls in blood pressure can occur.

Cessation of Therapy: If withdrawal of TENORMIN therapy is planned, it should be achieved gradually over a period of about 2 weeks. Patients should be carefully observed and advised to limit physical activity to a minimum.

HOW SUPPLIED: Tablets of 50 mg atenolol, NDC 0310-0105 (round, flat, uncoated white tablets identified with ICI debossed on one side and 105 debossed on the other side, bisected) are supplied in bottles of 100 tablets and unit-dose packages of 100 tablets.

Tablets of 100 mg atenolol, NDC 0310-0101 (round, flat, uncoated white tablets identified with ICI debossed on one side and 101 debossed on the other side) are supplied in bottles of 100 tablets and unit-dose packages of 100 tablets.

Protect from heat, light, and moisture.

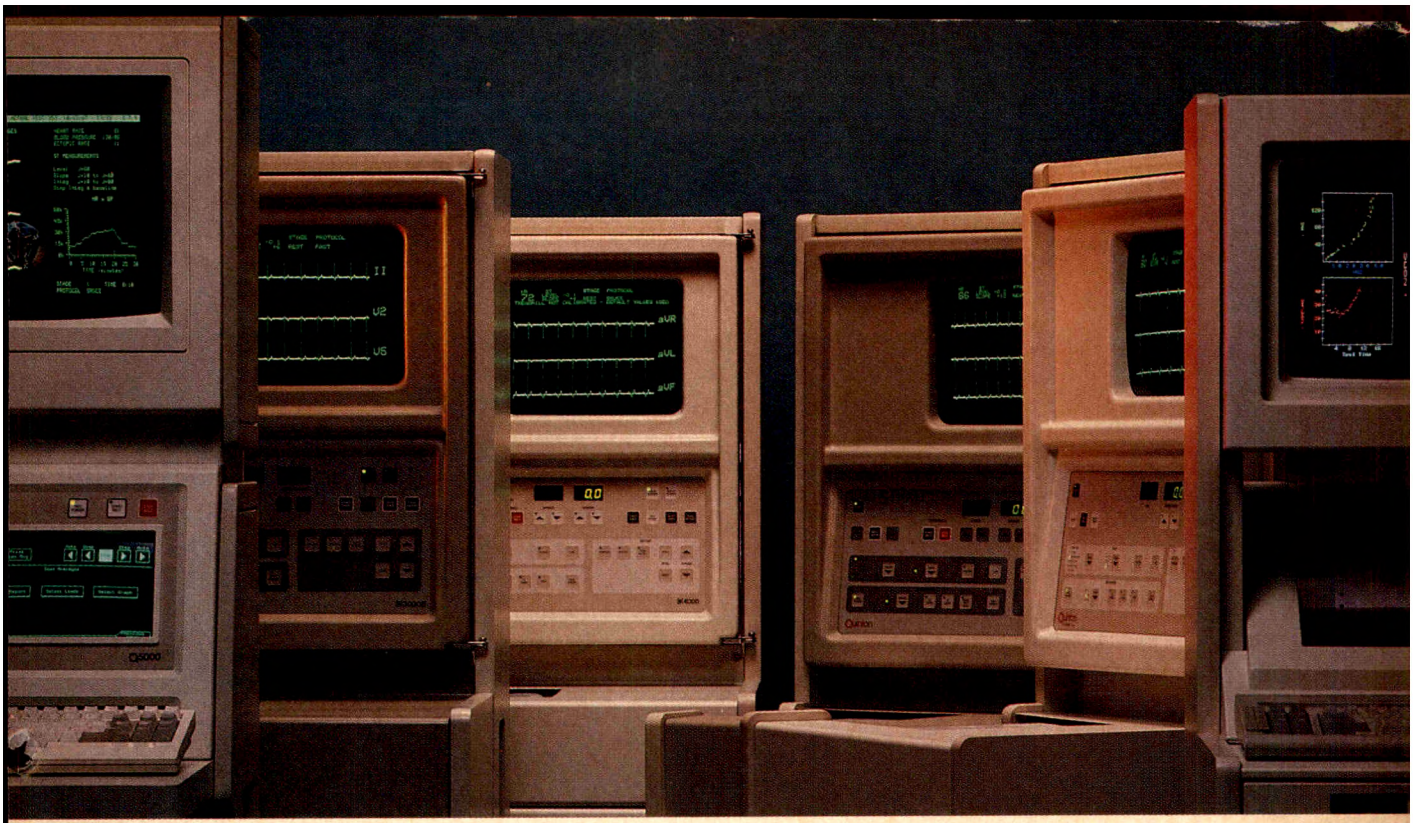
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The American Journal of Cardiology

JANUARY 1, 1990, VOL. 65, NO. 1

CORONARY ARTERY DISEASE

1

Dyslipidemias with Desirable Plasma Total Cholesterol Levels and Angiographically Demonstrated Coronary Artery Disease

Michael Miller, Lucy A. Mead, Peter O. Kwiterovich, Jr., and Thomas A. Pearson

A total cholesterol <200 mg/dl is "desirable" and no further evaluation of plasma lipoproteins is recommended based on guidelines established by the National Cholesterol Education Program. To examine dyslipidemias in a population with desirable cholesterol levels, 1,000 patients undergoing diagnostic coronary arteriography were evaluated. Of 288 patients with desirable cholesterol levels, approximately 67% of men with angiographically demonstrated coronary artery disease (CAD) and 80% of women with CAD had low levels of high density lipoprotein cholesterol (≤35 and ≤45 mg/dl, respectively) ($p < 0.05$). Multiple logistic regression analysis revealed that high density lipoprotein cholesterol in men and very low density lipoprotein cholesterol in women were associated with CAD after adjustment for other risk factors. These results suggest that all CAD patients should be screened for dyslipidemias, regardless of the plasma (or serum) total cholesterol level.

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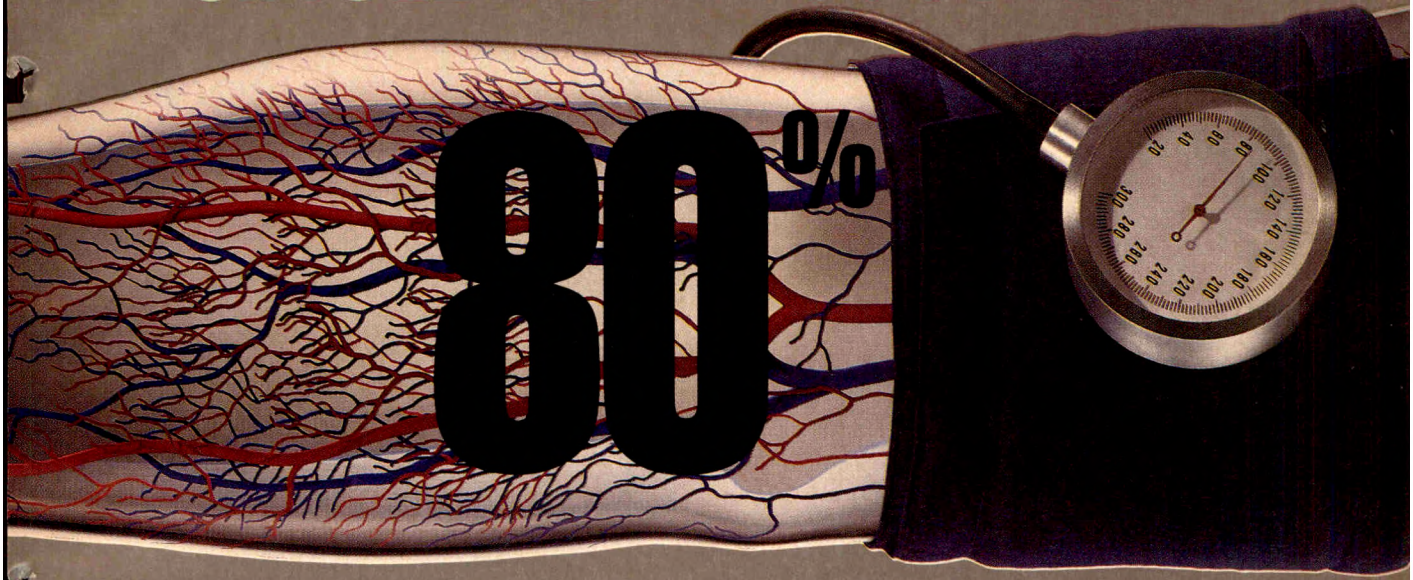
Blood Cholesterol Screening in Several Environments Using a Portable, Dry-Chemistry Analyzer and Fingerstick Blood Samples

Reagan H. Bradford, Paul S. Bachorik, Karen Roberts, O. Dale Williams, and Antonio M. Gotto, Jr., for the Lipid Research Clinics Cholesterol Screening Study Group

The 11 United States Lipid Research Clinics evaluated a portable, dry-chemistry analyzer using capillary blood for measuring cholesterol in several typical screening environments. Data are reported from a total of 13,824 participants, spanning the entire age spectrum. Overall, the proportion of referred screened subjects was at the expected level, but differed significantly among the screening environments and by gender. Follow-up telephone interviews indicated that >50% of the referrals had initiated a physician contact. Approximately 75% of those who had seen a physician reported that the diagnosis of hypercholesterolemia had been confirmed and a diet had been prescribed. A large proportion of referred screened subjects reported having modified their diets.

Continued on page A16

SINGLE-AGENT SUCCESS IN



OF HYPERTENSIVE PATIENTS*[1-6]

ONCE-A-DAY

Calan® SR

(verapamil HCl) 240mg

SUSTAINED-RELEASE **CAPLETS**

THE 80% SOLUTION

*In mild to moderate hypertension.

BRIEF SUMMARY

Contraindications: Severe LV dysfunction (see *Warnings*), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), hypersensitivity to verapamil.

Warnings: Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction < 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported. Several cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (2nd- and 3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol clearance may occur with combined use. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Concomitant use of lithium and verapamil may result in a lowering of serum lithium levels or increased sensitivity to lithium. Patients receiving both drugs must be monitored carefully. Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporin. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use.

Adverse Reactions: Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (2.5%), headache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4%), bradycardia: HR < 50/min (1.4%), AV block: total 1°,2°,3° (1.2%), 2° and 3° (0.8%), rash (1.2%), flushing (0.6%), elevated liver enzymes. The following reactions, reported in 1.0% or less of patients, occurred under conditions where a causal relationship is uncertain: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme, blurred vision, gynecomastia, increased urination, spotty menstruation, impotence.

2/9/89 • A88-W5282V-1

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A89-W8246T

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13

Relation of Silent Myocardial Ischemia After Coronary Artery Bypass Grafting to Angiographic Completeness of Revascularization and Long-Term Prognosis

Harold L. Kennedy, Sondra M. Seiler, Michael K. Sprague, Sharon M. Homan, James A. Whitlock, Morton J. Kern, Michel G. Vandormael, Hendrick B. Barner, John E. Codd, and Vallee L. Willman, with the technical assistance of Debra Lyyski

To assess the prevalence and characteristics of ambulatory electrocardiographic silent ischemia and examine its relation to angiographic revascularization and long-term outcome after coronary artery bypass grafting (CABG), 94 patients at 1 to 3 months after CABG and 184 patients at 12 months after CABG were examined by 24-hour ambulatory electrocardiography. Silent ischemia was detected in 20% of patients examined early and in 27% of patients examined late. Ambulatory electrocardiographic silent ischemia was not found to be associated with graft or anastamotic site occlusions, low graft flow rates, grafted vessels with significant distal residual stenoses or ungrafted stenotic native vessels. Kaplan-Meier and Cox regression analysis of 30 covariates failed to detect an increased risk of an adverse clinical outcome associated with silent ischemia during a mean follow-up of 48 ± 11 months.

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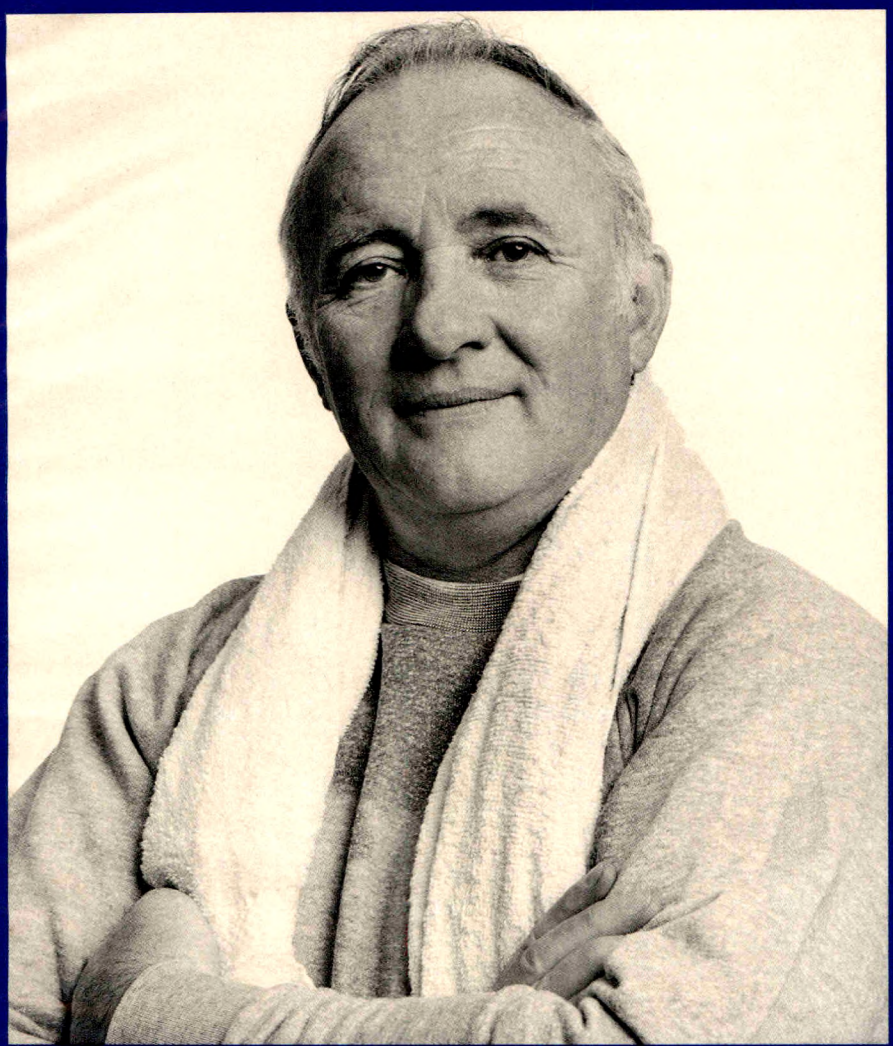
Frequency and Significance of Late Evolution of Q Waves in Patients with Initial Non-Q-Wave Acute Myocardial Infarction

Robert E. Kleiger, William E. Boden, Kenneth B. Schechtman, Robert S. Gibson, David J. Schwartz, Barbara J. Geiger, Robert J. Capone, Robert Roberts, and the Diltiazem Reinfarction Study Group

Five hundred forty-four patients with non-Q-wave acute myocardial infarcts randomized to a diltiazem–placebo–controlled therapeutic trial had sequential electrocardiograms and repetitive measurements of CK-MB enzymes to assess the proportion of patients who developed Q waves after randomization to trial and the relation between Q-wave development and extension of infarct. Seventy-six patients (14%) developed late Q waves. Fourteen of these patients also had extension as determined by secondary increases in CK-MB. Patients who developed Q waves had higher peak CK-MB levels at entry, were more likely to have ST elevation on their presenting electrocardiogram, and had significantly higher percentage of extensions, although the majority of patients did not extend. Most Q waves developed between 2 days of study entry (mean time at entry 50 ± 10 hours). No clinical or electrocardiographic variable showed high predictive value for the development of Q waves.

Continued on page A20

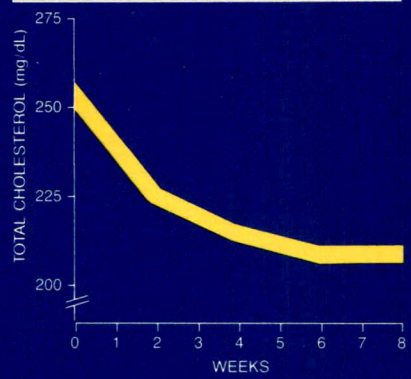
Who's getting results on MEVACOR®?
(LOVASTATIN | MSD)



Patient D.M.

- Male, age 58
- Two years post-myocardial infarction
- Elevated total cholesterol of 255 mg/dL after adequate trial of a cholesterol-lowering diet
- After 6 weeks on MEVACOR, total cholesterol is 209 mg/dL (dosage: 20 mg once daily with the evening meal)

Results with MEVACOR



Not everyone will respond as did the patient in this hypothetical case history; however, the mean reduction in total cholesterol in clinical trials was 17% at 20 mg once a day and 27% at 20 mg b.i.d.

MEVACOR is indicated as an adjunct to diet for the reduction of elevated total and LDL cholesterol levels in patients with primary hypercholesterolemia (Types IIa and IIb) when response to nonpharmacologic measures has been inadequate.

MEVACOR is contraindicated in patients who are hypersensitive to any component of the medication; in patients with active liver disease or unexplained persistent transaminase elevations; in pregnant or lactating patients; and in women of childbearing age, except when such patients are highly unlikely to conceive.

It is recommended that liver function tests be performed before treatment begins, every 4 to 6 weeks during the first 15 months of therapy, and periodically thereafter in all patients.

The effect of lovastatin-induced changes in serum lipoprotein levels, including reduction of serum cholesterol, on cardiovascular morbidity or mortality has not been established.

For more details on warnings, precautions, and adverse reactions, including cautionary information regarding liver dysfunction, myopathy, and slit-lamp monitoring, please see Prescribing Information.

For a Brief Summary of Prescribing Information, please see the following page.

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TABLETS, 20mg and 40mg

MSD
MERCK SHARP & DOHME

MEVACOR®
(LOVASTATIN | MSD)



CONTRAINDICATIONS: Hypersensitivity to any component of this medication.

Active liver disease or unexplained persistent elevations of serum transaminases.

Pregnancy and lactation.

Atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Moreover, cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development, including synthesis of steroids and cell membranes. Because of the ability of inhibitors of HMG-CoA reductase such as MEVACOR® (Lovastatin, MSD) to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway, MEVACOR may cause fetal harm when administered to a pregnant woman. Therefore, lovastatin is contraindicated during pregnancy. Lovastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive. If the patient becomes pregnant while taking this drug, lovastatin should be discontinued and the patient should be apprised of the potential hazard to the fetus.

WARNINGS: ***Liver Dysfunction:*** **Marked persistent increases (to more than 3 times the upper limit of normal) in serum transaminases occurred in 1.9% of adult patients who received lovastatin for at least one year in clinical trials (see ADVERSE REACTIONS).** When the drug was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pretreatment levels. The increases usually appeared 3 to 12 months after the start of therapy with lovastatin and were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity. A liver biopsy was done in one of these patients and showed areas of focal hepatitis. In this patient, transaminase levels returned to normal following discontinuation of therapy. Some of these patients had abnormal liver function tests prior to lovastatin therapy and/or consumed substantial quantities of alcohol.

It is recommended that liver function tests be performed before treatment begins, every 4 to 6 weeks during the first 15 months of therapy with lovastatin, and periodically thereafter in all patients. Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 times the upper limit of normal and are persistent, the drug should be discontinued. Liver biopsy should be considered if elevations are persistent beyond the discontinuation of the drug.

The drug should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver disease or unexplained transaminase elevations are contraindications to the use of lovastatin.

As with other lipid-lowering agents, moderate (less than 3 times the upper limit of normal) elevations of serum transaminases have been reported following therapy with MEVACOR (see ADVERSE REACTIONS). These changes appeared soon after initiation of therapy with MEVACOR, were often transient, were not accompanied by any symptoms, and interruption of treatment was not required.

Skeletal Muscle: **Several cases of rhabdomyolysis have been associated with lovastatin therapy alone, when combined with immunosuppressive therapy including cyclosporine in cardiac transplant patients, and when combined in non-transplant patients with either gemfibrozil or lipid-lowering doses (≥ 1 g/day) of nicotinic acid. Acute renal failure from rhabdomyolysis has been seen more commonly with the lovastatin-gemfibrozil combination and has also been reported in transplant patients receiving lovastatin plus cyclosporine.**

Rhabdomyolysis with or without renal impairment has been reported in seriously ill patients receiving erythromycin concomitantly with lovastatin. Therefore, patients receiving concomitant lovastatin and erythromycin should be carefully monitored.

Fulminant rhabdomyolysis has been seen as early as 3 weeks after initiation of combined therapy with gemfibrozil and lovastatin but may be seen after several months. For these reasons, it is felt that in most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefits of combined therapy with lovastatin and gemfibrozil do not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. While it is not known whether this interaction occurs with fibrates other than gemfibrozil, myopathy and rhabdomyolysis have occasionally been associated with the use of other fibrates alone, including clofibrate. Therefore, the combined use of lovastatin with other fibrates should generally be avoided.

Physicians contemplating combined therapy with lovastatin and lipid-lowering doses of nicotinic acid or with immunosuppressive drugs should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic CPK determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy. The monitoring of lovastatin drug and metabolite levels may be considered in transplant patients who are treated with immunosuppressives and lovastatin.

Lovastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis, including severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine, and electrolyte disorders, and uncontrolled seizures.

Myalgia has been associated with lovastatin therapy. Transient, mildly elevated creatine phosphokinase levels are commonly seen in lovastatin-treated patients. However, in clinical trials, approximately 0.5% of patients developed a myopathy, i.e., myalgia or muscle weakness associated with markedly elevated CPK levels. Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. Lovastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

Most of the patients who have developed myopathy (including rhabdomyolysis) while taking lovastatin were receiving concomitant therapy with immunosuppressive drugs, gemfibrozil, or lipid-lowering doses of nicotinic acid. In clinical trials, about 30% of patients on concomitant immunosuppressive therapy including cyclosporine developed myopathy; the corresponding percentages for gemfibrozil and niacin were approximately 5% and 2%, respectively.

In 6 patients with cardiac transplants taking immunosuppressive therapy including cyclosporine concomitantly with lovastatin 20 mg/day, the average plasma level of active metabolites derived from lovastatin was elevated to approximately 4 times the expected levels. Because of an apparent relationship between increased plasma levels of active metabolites derived from lovastatin and myopathy, the daily dosage in patients taking immunosuppressants should not exceed 20 mg/day (see DOSAGE AND ADMINISTRATION). Even at this dosage, the benefits and risks of using lovastatin in patients taking immunosuppressants should be carefully considered.

PRECAUTIONS: ***General:*** Before instituting therapy with MEVACOR® (Lovastatin, MSD), an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, weight reduction in obese patients, and to treat other underlying medical problems (see INDICATIONS AND USAGE).

Lovastatin may elevate creatine phosphokinase and transaminase levels (see ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with lovastatin.

Eye: There was a high prevalence of baseline lenticular opacities in the patient population included in the clinical trials with lovastatin. During these trials the appearance of new opacities was noted. The causal relationship of lovastatin to these findings has not been established.

Of 431 patients examined with slit lamp at baseline and during therapy with lovastatin, 34 had opacities reported at the final examination (5 to 15 months after starting lovastatin) that were not noted at baseline. On the other hand, in 45 patients, opacities observed at baseline were not noted at the final examination, so that the prevalence did not increase. There was no clinically significant change in visual acuity in the patients who had new opacities reported, nor was any patient, including those with opacities noted at baseline, discontinued from therapy because of a decrease in visual acuity. Nevertheless, until further experience is obtained, it is recommended that patients placed on lovastatin therapy be examined with a slit lamp before or shortly after initiation of treatment and annually thereafter.

Homozygous Familial Hypercholesterolemia: MEVACOR is less effective in patients with the rare homozygous familial hypercholesterolemia, possibly because these patients have no functional LDL receptors. MEVACOR appears to be more likely to raise serum transaminases (see ADVERSE REACTIONS) in these homozygous patients.

Drug Interactions: *Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin:* See WARNINGS, *Skeletal Muscle.*

Coumarin Anticoagulants: In a clinical trial in warfarin-treated patients designed specifically to observe a potential effect of lovastatin on the prothrombin time, lovastatin in dosages up to 40 mg b.i.d. did not produce any consistent alteration of the anticoagulant action of warfarin. However, since the drug was marketed, clinically evident bleeding and/or increased prothrombin time have been reported in a few patients taking coumarin anticoagulants concomitantly with lovastatin. The causal relationship to lovastatin is unclear. Nevertheless, it is recommended that in patients taking anticoagulants, prothrombin time be determined before starting lovastatin and frequently enough during early therapy to insure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of lovastatin is changed, the same procedure should be repeated. Lovastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Antipyrine: Antipyrine is a model for drugs metabolized by the microsomal hepatic enzyme system (cytochrome P450 system). Because lovastatin had no effect on the pharmacokinetics of antipyrine, interactions with other drugs metabolized via this mechanism are not expected.

Propranolol: In normal volunteers, there was no clinically significant pharmacokinetic or pharmacodynamic interaction with concomitant administration of single doses of lovastatin and propranolol.

Digoxin: In patients with hypercholesterolemia, concomitant administration of lovastatin and digoxin resulted in no effect on digoxin plasma concentrations.

Other Concomitant Therapy: Although specific interaction studies were not performed, in clinical studies, lovastatin was used concomitantly with beta blockers, calcium channel blockers, diuretics, and nonsteroidal anti-inflammatory drugs (NSAIDs) without evidence of clinically significant adverse interactions.

Carcinogenesis, Mutagenesis, Impairmeat of Fertility: In a 21-month carcinogenic study in mice, a statistically significant ($p<0.05$) increase in the incidence of hepatocellular carcinomas and adenomas was observed at doses of 500 mg/kg/day (312 times the maximum recommended human dose) of lovastatin. These changes were not seen in mice given doses of 20 and 100 mg/kg/day (12.5 and 62.5 times the maximum recommended human dose).

A statistically significant increase ($p\leq 0.05$) in the incidence of pulmonary adenomas was seen in female mice receiving 500 mg/kg/day (312 times the maximum recommended human dose); no similar changes were seen in males at any dose or in females receiving 20 or 100 mg/kg/day (12.5 or 62.5 times the maximum recommended human dose). Because the incidence of pulmonary tumors was within the range of untreated animals in studies of similar duration, the relationship of this latter change to treatment is not known.

In addition, an increase in the incidence of papilloma in the non-glandular mucosa of the stomach was observed in mice receiving 100 and 500 mg/kg/day (62.5 and 312 times the maximum recommended human dose); no increase was seen at a dosage of 20 mg/kg/day (12.5 times the maximum recommended human dose). The glandular mucosa was not affected. The human stomach contains only glandular mucosa. Importantly, there is a strong association between this change and hyperplasia of the squamous epithelium (acanthosis) in this region; acanthosis is a characteristic change observed in the non-glandular mucosa of rodents treated with HMG-CoA reductase inhibitors and is most probably a result of inhibition of the reductase in this tissue.

Similar squamous epithelium is found in the esophagus and anorectal junction of the mouse and rat; however, no evidence of a similar drug-induced hyperplastic response was observed in these tissues in studies of up to 21 months in the mouse given up to 500 mg/kg/day (312 times the maximum recommended human dose), or in a study of 24 months in the rat given 180 mg/kg/day (112 times the maximum recommended human dose).

In a 24-month carcinogenicity study in rats, there was a positive dose response relationship for hepatocellular carcinogenicity in males (unadjusted $p=0.025$). However, because the incidence of hepatocellular carcinogenicity observed in male rats in this study is similar to that observed spontaneously in this strain of rat, the implications of this finding are unclear.

No evidence of mutagenicity was observed in a microbial mutagen test using mutant strains of *Salmonella typhimurium* with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an *in vitro* alkaline elution assay using rat or mouse hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosomal aberration assay in mouse bone marrow.

No drug-related effects on fertility were found in studies with rats.

Pregnancy: Pregnancy Category X: See CONTRAINDICATIONS.

Lovastatin has been shown to produce skeletal malformations in the rat fetus at doses of 800 mg/kg/day (500 times the maximum recommended human dose). At similar doses in mice, an increase in skeletal malformations was observed. These individual changes are within the range of those observed spontaneously in this strain of mouse. No drug-induced changes were seen in either species at doses of up to 80 mg/kg/day (50 times the maximum recommended human dose). No evidence of malformations was noted in rabbits at up to 15 mg/kg/day (highest tolerated dose –about 9 times the maximum recommended human dose). There are no data in pregnant women.

Nursing Mothers: Studies in rats have shown that lovastatin is excreted in the milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from MEVACOR, women taking lovastatin should not nurse their infants (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in children have not been established. Because children are not likely to benefit from cholesterol lowering for at least a decade and because experience with this drug is limited (no studies in subjects below the age of 20 years), treatment of children with lovastatin is not recommended at this time.

ADVERSE REACTIONS: MEVACOR® (Lovastatin, MSD) is generally well tolerated; adverse reactions usually have been mild and transient. Less than 1% of patients were discontinued from controlled clinical studies due to adverse experiences attributable to MEVACOR. About 2% of patients were discontinued from all studies (controlled and uncontrolled) due to adverse experiences attributable to MEVACOR; about one-third of these patients were discontinued due to increases in serum transaminases.

Clinical Adverse Experiences: Adverse experiences reported in patients treated with MEVACOR in controlled clinical studies are shown in the table below:

	MEVACOR (N = 613) %	Placebo (N = 82) %	Cholestyramine (N = 88) %	Probucol (N = 97) %
Gastrointestinal				
Constipation	4.9	—	34.1	2.1
Diarrhea	5.5	4.9	8.0	10.3
Dyspepsia	3.9	—	13.6	3.1
Flatus	6.4	2.4	21.6	2.1
Abdominal pain/cramps	5.7	2.4	5.7	5.2
Heartburn	1.6	—	8.0	—
Nausea	4.7	3.7	9.1	6.2
Musculoskeletal				
Muscle cramps	1.1	—	1.1	—
Myalgia	2.4	1.2	—	—
Nervous System/Psychiatric				
Dizziness	2.0	1.2	—	1.0
Headache	9.3	4.9	4.5	8.2
Skin				
Rash/pruritus	5.2	—	4.5	—
Special Senses				
Blurred vision	1.5	—	1.1	3.1
Dysgeusia	0.8	—	1.1	—

Laboratory Tests: Marked persistent increases of serum transaminases have been noted (see WARNINGS).

About 11% of patients had elevations of creatine phosphokinase (CPK) levels of at least twice the normal value on one or more occasions. The corresponding values for the control agents were cholestyramine, 9% and probucol, 2%. This was attributable to the noncardiac fraction of CPK. Large increases in CPK have sometimes been reported (see WARNINGS, *Skeletal Muscle*).

Concomitant Therapy: In controlled clinical studies in which lovastatin was administered concomitantly with cholestyramine, no adverse reactions peculiar to this concomitant treatment were observed. The adverse reactions that occurred were limited to those reported previously with lovastatin or cholestyramine. Other lipid-lowering agents were not administered concomitantly with lovastatin during controlled clinical studies. In uncontrolled clinical studies, most of the patients who have developed myopathy were receiving concomitant therapy with immunosuppressive drugs, gemfibrozil, or niacin (nicotinic acid) (see WARNINGS, *Skeletal Muscle*).

Uncontrolled Clinical Studies: The adverse experiences observed in uncontrolled studies were similar to those seen in controlled clinical studies. Abnormal liver function tests were observed at a higher incidence than in the controlled studies (see WARNINGS, *Liver Dysfunction*). Myopathy (myalgia with marked CPK elevations) was reported in approximately 0.5% of patients (see WARNINGS, *Skeletal Muscle*).

Causal Relationship Unclear: *Nervous System:* Peripheral neuropathy has been reported; the relationship to lovastatin is uncertain. Visual evoked response, nerve conduction measurements, and electromyography in over 30 patients showed no evidence of neurotoxic effects of lovastatin.

Special Senses: Of 431 patients examined with slit lamp at baseline and during therapy with lovastatin, 34 had opacities reported at the final examination (5 to 15 months after starting lovastatin) that were not noted at baseline. On the other hand, in 45 patients, opacities observed at baseline were not noted at the final examination, so that the prevalence did not increase (see PRECAUTIONS).

Post-marketing Experience: Additional adverse experiences occurring since the drug was marketed are listed below:

Clinical Adverse Experiences

Gastrointestinal: Hepatitis, cholestatic jaundice, anorexia, vomiting.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus-like syndrome, polymyalgia rheumatica, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, and malaise.

Nervous System/Psychiatric: Psychic disturbances, including anxiety; paresthesia.

Causal Relationship Unknown

Gastrointestinal: Pancreatitis, stomatitis.

Skin: Alopecia.

Nervous System/Psychiatric: Depression, insomnia.

Metabolic: Edema.

Clinical Laboratory Test Findings

Liver Function Tests: Liver function test abnormalities, including elevated alkaline phosphatase and bilirubin.

OVERDOSAGE: The oral LD_{50} of MEVACOR in mice is 20 g/kg.

Five healthy human volunteers have received up to 200 mg of lovastatin as a single dose without clinically significant adverse experiences. A few cases of accidental overdosage have been reported; no patients had any specific symptoms, and all patients recovered without sequelae. The maximum dose taken was 52 20-mg tablets (1.04 g).

Until further experience is obtained, no specific treatment of overdosage with MEVACOR can be recommended.

The dialyzability of lovastatin and its metabolites in man is not known at present.

DOSAGE AND ADMINISTRATION: The patient should be placed on a standard cholesterol-lowering diet before receiving MEVACOR and should continue on this diet during treatment with MEVACOR. MEVACOR should be given with meals.

The recommended starting dose is 20 mg once a day given with the evening meal. The recommended dosing range is 20 to 80 mg/day in single or divided doses; the maximum recommended dose is 80 mg/day. Adjustments of dosage should be made at intervals of 4 weeks or more. Doses should be individualized according to the patient's response (see Tables I to IV under CLINICAL PHARMACOLOGY, *Clinical Studies* for dose response results).

For those patients with severely elevated serum cholesterol levels (i.e., >300 mg/dL [7.8 mmol/L] on diet), MEVACOR may be initiated at 40 mg/day.

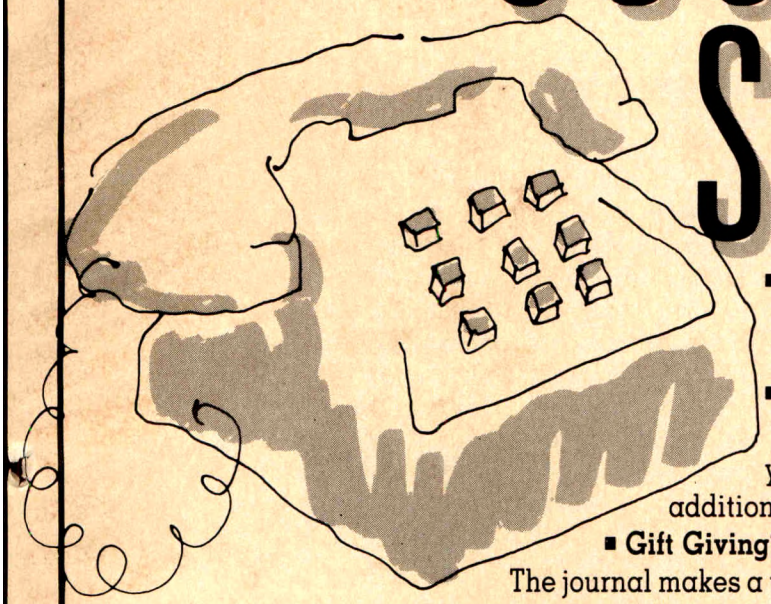
In patients taking immunosuppressive drugs concomitantly with lovastatin (see WARNINGS, *Skeletal Muscle*), the maximum recommended dosage is 20 mg/day.

Cholesterol levels should be monitored periodically and consideration should be given to reducing the dosage of MEVACOR if cholesterol levels fall below the targeted range.

MSD
MERCK SHARP & DOHME

For more detailed information, consult your MSD Representative or see Prescribing Information, Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486. J8MC29R(508)

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Detection of Restenosis After Elective Percutaneous Transluminal Coronary Angioplasty Using the Exercise Treadmill Test

James R. Bengtson, Daniel B. Mark, Michael B. Honan, David S. Rendall, Tomoaki Hinohara, Richard S. Stack, Mark A. Hlatky, Robert M. Califf, Kerry L. Lee, and David B. Pryor

To determine the value of a 6-month exercise treadmill test for detecting restenosis after elective percutaneous transluminal coronary angioplasty (PTCA), 308 consecutive successful PTCA patients without a recent myocardial infarction were studied. Restenosis occurred in 25% of the patients who had repeat angiography and a follow-up treadmill test. Five variables were associated with a higher risk of restenosis: recurrent angina, exercise-induced angina, a positive treadmill test, more exercise ST deviation and a lower maximum exercise heart rate. However, only exercise-induced angina, recurrent angina and a positive treadmill test were independent predictors of restenosis. Using a combination of these variables, patients at high and low risk for restenosis could be identified. The exercise treadmill test stratified the risk of restenosis after elective PTCA better than symptoms. Nevertheless, 20% of patients with restenosis had neither recurrent angina nor exercise-induced ischemia at follow-up. For more accurate detection of restenosis, the exercise treadmill test must be supplemented by a more definitive test.

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Usefulness of Coronary Angioplasty in Asymptomatic Patients

H. Vernon Anderson, J. David Talley, Alexander J.R. Black, Gary S. Roubin, John S. Douglas, and Spencer B. King, III

During a 7.5-year period, 6,545 patients underwent elective coronary angioplasty. We identified 114 patients (1.7%) who never had symptoms of myocardial ischemia. Exercise-induced silent myocardial ischemia was documented in 94% of them. Angioplasty was successful in 87%, whereas 4% required emergency coronary bypass surgery and a further 2% had myocardial infarctions. Another 7% had unsuccessful procedures but no in-hospital cardiac events. Complete follow-up ranged from 5 to 93 months. There were no deaths. In follow-up of the group of 99 patients with successful angioplasty, 7 patients underwent coronary bypass surgery, 4 patients had myocardial infarctions and 30 patients had repeat angioplasty for restenosis. Cumulative event-free survival over 5 years for the group with successful angioplasty was: 100% freedom from death, 95% freedom from myocardial infarction, 87% freedom from myocardial infarction or coronary bypass surgery and 61% freedom from myocardial infarction, coronary bypass surgery or repeat angioplasty. Thus, coronary angioplasty performed in 114 asymptomatic patients achieved very good primary success, with low cardiac event rates and no deaths over several years of follow-up. Future randomized trials will be required to confirm therapeutic benefit from coronary angioplasty in asymptomatic patients with coronary artery disease.

Continued on page A26

The only beta blocker as effective as quinidine

...without quinidine complications.

In randomized, double-blind crossover studies,[1,2] Sectral® (acebutolol HCl) was shown to be as effective as quinidine in reducing spontaneous premature ventricular contractions (PVCs), exercise-induced PVCs and complex PVCs.* Unlike quinidine, Sectral® was not associated with drug-related gastric discomfort or diarrhea.[1,2] Clinical experience in over 1,000 patients yielded only a 4 percent incidence of diarrhea, constipation or flatulence.

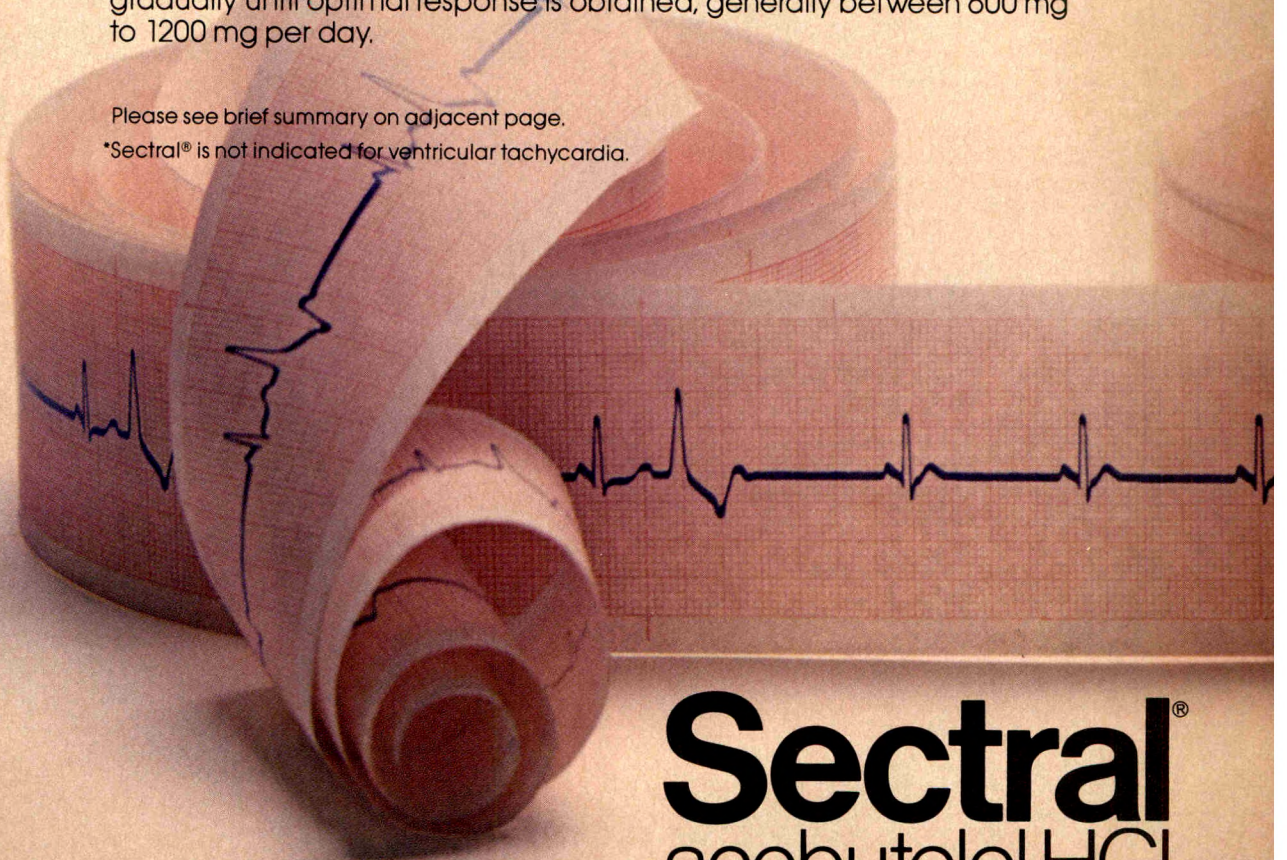
As the investigators commented: "The antiarrhythmic activity of (Sectral®), its ancillary pharmacologic properties, and its tolerance by a diverse group of patients make (Sectral®) a significant tool for the clinician in the management of chronic arrhythmia."[2]

Like other beta blockers, Sectral® is contraindicated in persistently severe bradycardia, second- and third-degree heart block, overt congestive heart failure and cardiogenic shock.

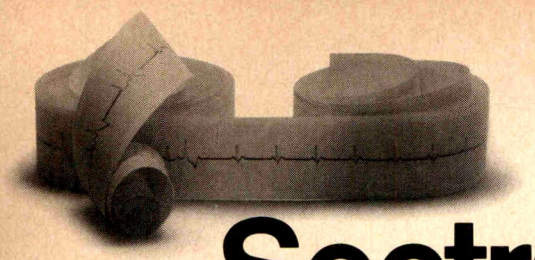
Initiate Sectral® therapy with 200 mg b.i.d. Dosage can be increased gradually until optimal response is obtained, generally between 600 mg to 1200 mg per day.

Please see brief summary on adjacent page.

*Sectral® is not indicated for ventricular tachycardia.



Sectral®
acebutolol HCl
For uncomplicated control of PVCs.



Sectral®
acebutolol HCl

For uncomplicated control of PVCs.

(Brief summary of prescribing information)

CONTRAINDICATIONS: SECTRAL is contraindicated in: 1) persistently severe bradycardia; 2)second- and third-degree heart block; 3) overt cardiac failure; and 4) cardiogenic shock. (See WARNINGS)

WARNINGS: CARDIAC FAILURE: Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by β-adrenergic receptor blockade may precipitate more severe failure. Although β-blockers should be avoided in overt cardiac failure, SECTRAL can be used with caution in patients with a history of heart failure who are controlled with digitalis and/or diuretics. Both digitalis and SECTRAL impair AV conduction. If cardiac failure persists, therapy with SECTRAL should be withdrawn.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE: In patients with aortic or mitral valve disease or compromised left ventricular function, continued depression of the myocardium with β-blocking agents over a period of time may lead to cardiac failure. At the first signs of failure, patients should be digitalized and/or be given a diuretic and the response observed closely. If cardiac failure continues despite adequate digitalization and/or diuretic, SECTRAL therapy should be withdrawn.

EXACERBATION OF ISCHEMIC HEART DISEASE FOLLOWING ABRUPT WITHDRAWAL: Following abrupt cessation of therapy with certain β-blocking agents in patients with coronary artery disease, exacerbation of angina pectoris and, in some cases, myocardial infarction and death have been reported. Therefore, such patients should be cautioned against interruption of therapy without a physician's advice. Even in the absence of overt ischemic heart disease, when discontinuation of SECTRAL is planned, the patient should be carefully observed, and should be advised to limit physical activity to a minimum while SECTRAL is gradually withdrawn over a period of about two weeks. (If therapy with an alternative β-blocker is desired, the patient may be transferred directly to comparable doses of another agent without interruption of β-blocking therapy). If an exacerbation of angina pectoris occurs, anti-anginal therapy should be restarted immediately in full doses and the patient hospitalized until his condition stabilizes.

PERIPHERAL VASCULAR DISEASE: Treatment with β-antagonists reduces cardiac output and can precipitate or aggravate the symptoms of arterial insufficiency in patients with peripheral or mesenteric vascular disease. Caution should be exercised with such patients and they should be observed closely for evidence of progression of arterial obstruction.

BRONCHOSPASTIC DISEASES: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD, IN GENERAL, NOT RECEIVE A β-BLOCKER. Because of its relative β_1-selectivity, however, low doses of SECTRAL may be used with caution in patients with bronchospastic disease who do not respond to, or who cannot tolerate, alternative treatment. Since β_1-selectivity is not absolute and is dose-dependent, the lowest possible dose of SECTRAL should be used initially, preferably in divided doses to avoid the higher plasma levels associated with the longer dose-interval. A bronchodilator, such as a theophylline or a β_2-stimulant, should be made available in advance with instructions concerning its use.

ANESTHESIA AND MAJOR SURGERY: The necessity, or desirability, of withdrawal of a β-blocking therapy prior to major surgery is controversial. β-adrenergic receptor blockade impairs the ability of the heart to respond to β-adrenergically mediated reflex stimuli. While this might be of benefit in preventing arrhythmic response, the risk of excessive myocardial depression during general anesthesia may be enhanced and difficulty in restarting and maintaining the heartbeat has been reported with beta-blockers. If treatment is continued, particular care should be taken when using anesthetic agents which depress the myocardium, such as ether, cyclopropane and trichlorethylene, and it is prudent to use the lowest possible dose of SECTRAL. SECTRAL, like other β-blockers, is a competitive inhibitor of β-receptor agonists and its effect on the heart can be reversed by cautious administration of such agents (e.g., dobutamine or isoproterenol—see OVERDOSE). Manifestations of excessive vagal tone (e.g., profound bradycardia, hypotension) may be corrected with atropine 1 to 3 mg i.v. in divided doses.

DIABETES AND HYPOGLYCEMIA: β-blockers may potentiate insulin-induced hypoglycemia and mask some of its manifestations such as tachycardia; however, dizziness and sweating are usually not significantly affected. Diabetic patients should be warned of the possibility of masked hypoglycemia.

THYROTOXICOSIS: β-adrenergic blockade may mask certain clinical signs (tachycardia) of hyperthyroidism. Abrupt withdrawal of β-blockade may precipitate a thyroid storm; therefore, patients suspected of developing thyrotoxicosis from whom SECTRAL therapy is to be withdrawn should be monitored closely.

PRECAUTIONS: IMPAIRED RENAL OR HEPATIC FUNCTION: Studies on the effect of acebutolol in patients with renal insufficiency have not been performed in the U.S. Foreign published experience shows that acebutolol has been used successfully in chronic renal insufficiency. Acebutolol is excreted through the G.I. tract, but the active metabolite, diacetolol, is eliminated predominantly by the kidney. There is a linear relationship between renal clearance of diacetolol and creatinine clearance. Therefore, the daily dose of acebutolol should be reduced by 50% when the creatinine clearance is less than 50 mL/min and by 75% when it is less than 25 mL/min. SECTRAL should be used cautiously in patients with impaired hepatic function.

SECTRAL has been used successfully and without problems in elderly patients in the U.S. clinical trials without specific adjustment of dosage. However, elderly patients may require lower maintenance doses because the bioavailability of both SECTRAL and its metabolite are approximately doubled in this age group.

CLINICAL LABORATORY FINDINGS: SECTRAL, like other β-blockers, has been associated with the development of antinuclear antibodies (ANA). In prospective clinical trials, patients receiving SECTRAL had a dose dependent increase in the development of positive ANA titers and the overall incidence was higher than that observed with propranolol. Symptoms (generally persistent arthralgias and myalgias) related to this laboratory abnormality were infrequent (less than 1% with both drugs). Symptoms and ANA titers were reversible upon discontinuation of treatment.

INFORMATION FOR PATIENTS: Patients, especially those with evidence of coronary artery disease, should be warned against interruption or discontinuation of SECTRAL therapy without a physician's supervision. Although cardiac failure rarely occurs in properly selected patients, those being treated with β-adrenergic blocking agents should be advised to consult a physician if they develop signs or symptoms suggestive of impending CHF, or unexplained respiratory symptoms.

Patients should also be warned of possible severe hypertensive reactions from concomitant use of α-adrenergic stimulants such as the nasal decongestants commonly used in OTC cold preparations and nasal drops.

DRUG INTERACTIONS: Catecholamine-depleting drugs, such as reserpine, may have an additive effect when given with β-blocking agents. Patients treated with SECTRAL plus catecholamine depletors should, therefore, be observed closely for evidence of marked bradycardia or hypotension which may present as vertigo, syncope/pre-syncope, or orthostatic changes in blood pressure without compensatory tachycardia. Exaggerated hypertensive responses have been reported from the combined use of β-adrenergic antagonists and α-adrenergic stimulants, including those contained in proprietary cold remedies and vasoconstrictive nasal drops. Patients receiving β-blockers should be warned of this potential hazard. No significant interactions with digoxin, hydrochlorothiazide, hydralazine, sulfinpyrazone, oral contraceptives, tolbutamide or warfarin have been observed.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Chronic oral toxicity studies in rats and mice, employing dose levels as high as 300 mg/kg/day, which is equivalent to 15 times the maximum recommended (60 kg) human dose, did not indicate a carcinogenic potential for SECTRAL (acebutolol HCl). Diacetolol, the major metabolite of SECTRAL in man, was without carcinogenic potential in rats when tested at doses as high as 1800 mg/kg/day. SECTRAL and diacetolol were also shown to be devoid of mutagenic potential in the Ames Test. SECTRAL, administered orally to two generations of male and female rats at doses of up to 240 mg/kg/day [equivalent to 12 times the maximum recommended therapeutic dose in (a 60 kg) man] and diacetolol, administered to two generations of male and female rats at doses of up to 1000 mg/kg/day, had no significant impact on reproductive performance or fertility.

TERATOGENIC EFFECTS: *Pregnancy Category B*: Reproduction studies have been performed with SECTRAL in rats and rabbits at doses of up to 60 mg/kg/day, the equivalent of 3 times the maximum recommended therapeutic dose in (a 60 kg) man. Studies have also been performed in these species with diacetolol (at doses of up to 450 mg/kg/day in rabbits and up to 1800 mg/kg/day in rats). Other than a significant elevation in postimplantation loss with 450 mg/kg/day diacetolol, a level at which food consumption and body weight gain was reduced in rabbit dams and a non-statistically significant increase in incidence of bilateral cataract in rat fetuses from dams treated with 1800 mg/kg/day diacetolol, there was no evidence of harm to the fetus with either drug. There are no adequate and well-controlled trials in pregnant women in the U.S.; however, studies have shown that both acebutolol and diacetolol cross the placenta. Because animal teratology studies are not always predictive of the human response, SECTRAL should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

Labor and Delivery: The effect of SECTRAL on labor and delivery in pregnant women is unknown. Studies in animals have not shown any effect of SECTRAL on the usual course of labor and delivery.

Nursing Mothers: Acebutolol and diacetolol also appear in breast milk with a milk:plasma ratio of 7.1 and 12.2, respectively. Use in nursing mothers is not recommended.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: SECTRAL is well tolerated in properly selected patients. Most adverse reactions have been mild, not required discontinuation of therapy, and tended to decrease as duration of treatment increases.

The following table shows the frequency of treatment-related side effects derived from controlled clinical trials in patients with hypertension, angina pectoris, and arrhythmia. These patients received SECTRAL, propranolol, or hydrochlorothiazide as monotherapy, or placebo.

TOTAL VOLUNTEERED AND ELICITED (U.S. STUDIES)

Body System/ Adverse Reaction	SECTRAL (N=1002) %	Propranolol (N=424) %	Hydrochlorothiazide (N=178) %	Placebo (N=314) %
Cardiovascular				
Chest Pain	2	4	4	1
Edema	2	2	4	1
Central Nervous System				
Depression	2	1	3	1
Dizziness	6	7	12	2
Fatigue	11	17	10	4
Headache	6	9	13	4
Insomnia	3	6	5	1
Abnormal dreams	2	3	0	1
Dermatologic				
Rash	2	2	4	1
Gastrointestinal				
Constipation	4	2	7	0
Diarrhea	4	5	5	1
Dyspepsia	4	6	3	1
Flatulence	3	4	7	1
Nausea	4	6	3	0
Genitourinary				
Micturition (frequency)	3	1	9	<1
Musculoskeletal				
Arthralgia	2	1	3	2
Myalgia	2	1	4	0
Respiratory				
Cough	1	1	2	0
Dyspnea	4	6	4	2
Rhinitis	2	1	4	<1
Special Senses				
Abnormal Vision	2	2	3	0

The following selected (potentially important) side effects were seen in up to 2% of SECTRAL patients: *Cardiovascular*: hypotension, bradycardia, heart failure. *Central Nervous System*: anxiety, hyper/hypoesthesia, impotence. *Dermatological*: pruritus. *Gastrointestinal*: vomiting, abdominal pain. *Genitourinary*: dysuria, nocturia. *Musculoskeletal*: back pain, joint pain. *Respiratory*: pharyngitis, wheezing. *Special Senses*: conjunctivitis, dry eye, eye pain.

The incidence of drug-related adverse effects (volunteered and solicited) according to SECTRAL dose is shown below. (Data from 266 hypertensive patients treated for 3 months on a constant dose.)

Body System	400 mg/ day (N=132)	800 mg/ day (N=63)	1200 mg/ day (N=71)
Cardiovascular	5%	2%	1%
Gastrointestinal	3%	3%	7%
Musculoskeletal	2%	3%	4%
Central Nervous System	9%	13%	17%
Respiratory	1%	5%	6%
Skin	1%	2%	1%
Special Senses	2%	2%	6%
Genitourinary	2%	3%	1%

POTENTIAL ADVERSE EFFECTS: In addition, certain adverse effects not listed above have been reported with other β-blocking agents and should also be considered as potential adverse effects of SECTRAL.

Central Nervous System: Reversible mental depression progressing to catatonia (an acute syndrome characterized by disorientation for time and place), short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance (neuropsychometrics).

Cardiovascular: Intensification of AV block (see CONTRAINDICATIONS).

Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm, and respiratory distress.

Hematologic: Agranulocytosis, non-thrombocytopenic, and thrombocytopenic purpura.

Gastrointestinal: Mesenteric arterial thrombosis and ischemic colitis.

Miscellaneous: Reversible alopecia and Peyronie's disease. The oculomucocutaneous syndrome associated with the β-blocker practolol has not been reported with SECTRAL during investigational use and extensive foreign clinical experience.

Keep at room temperature. Approximately 25°C (77°F).

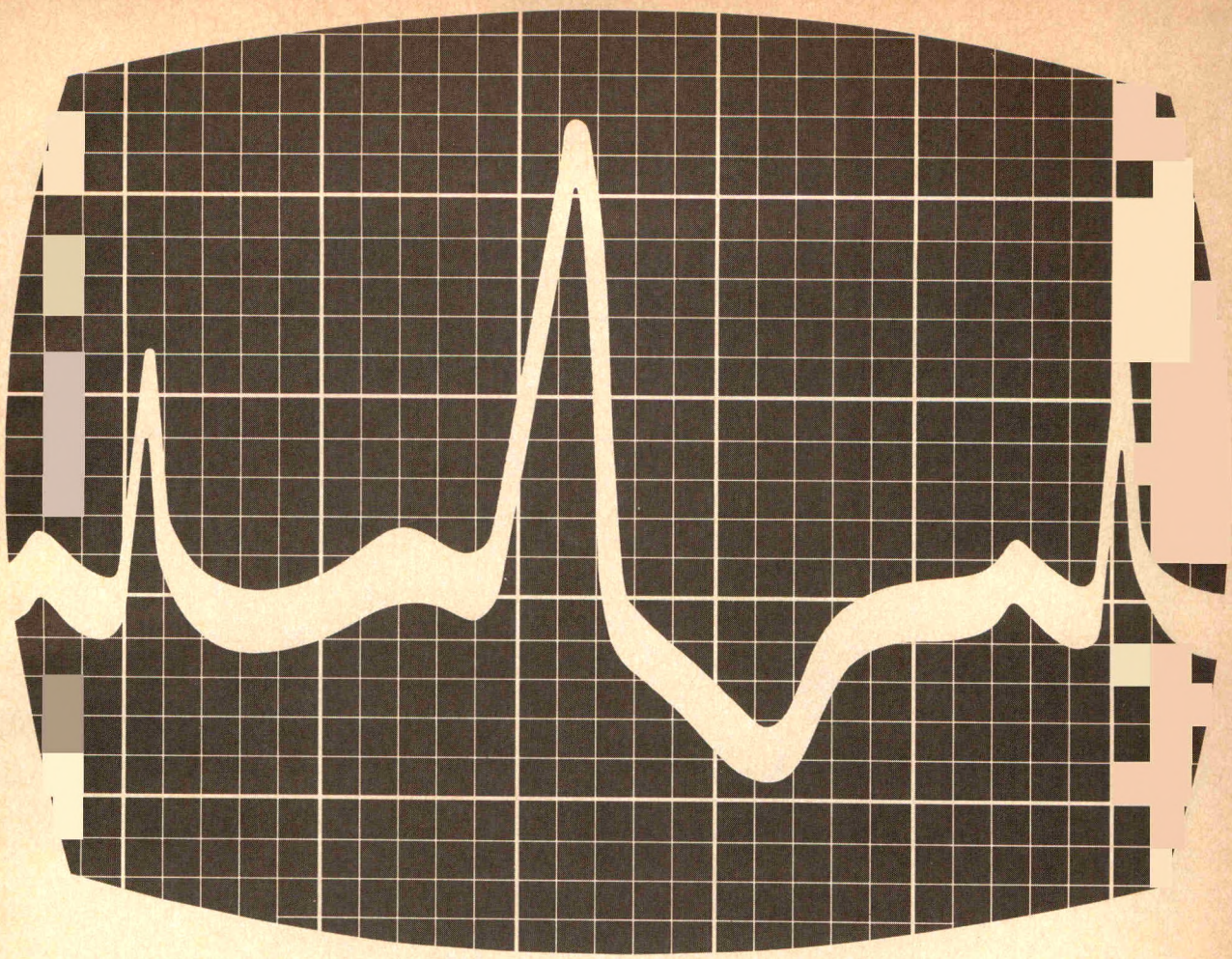
*Sectral® is not indicated in ventricular tachycardia.

References

1. Shapiro W, Park J, Koch GG: Variability of spontaneous and exercise-induced ventricular arrhythmias in the absence and presence of treatment with acebutolol or quinidine. *Am J Cardiol* 1982;49:445-454.
2. Chandraratna PAN: Comparison of acebutolol with propranolol, quinidine, and placebo: Results of three multicenter arrhythmia trials. *Am Heart J* 1985;109:1198-1204.

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PVC OR P.C.P.?

(Angel Dust)

The physiological and psychological symptoms of substance abuse can mimic an astounding range of systemic disorders.

Even more frightening is the fact that illegal drugs can cause sudden death *before* any symptoms occur – regardless of the dose, blood levels, or route of administration.

Help your patients stop illegal drug use before it stops them. Ask about abuse as a routine part of your examination.

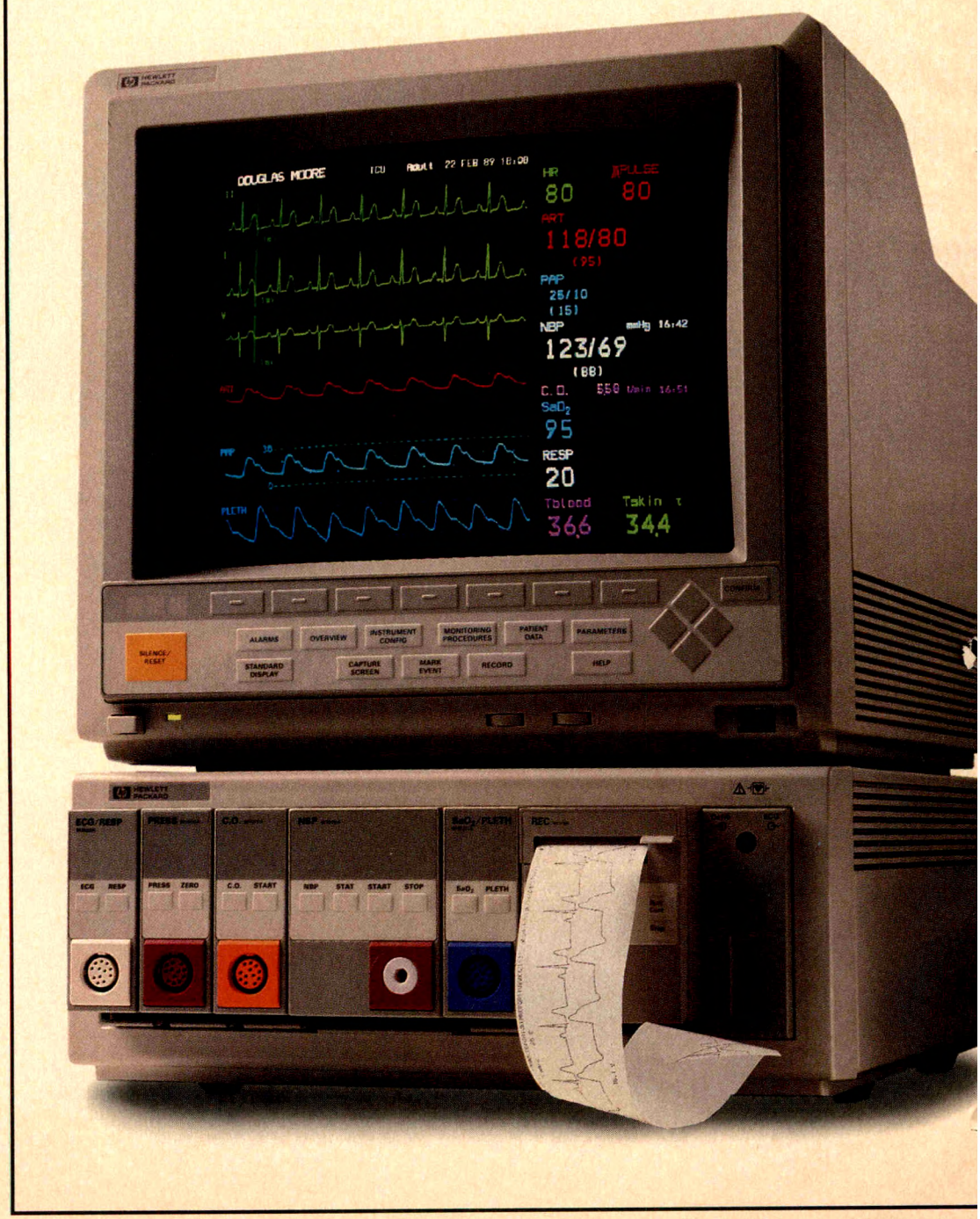
For information, healthcare professionals may call the National Clearinghouse for Alcohol and Drug Abuse: 1-301-468-2600, Monday through Friday, 8:30 AM – 4:30 PM EST.

HELP STOP SUBSTANCE ABUSE.
ASK THE QUESTIONS.

Partnership for a Drug-Free America

MC-9

Simply Revolutionary.



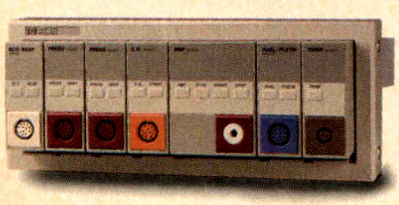
Mix and match patient parameter modules, racks, printers, recorders, and displays.

Modular components separate so you can customize system to your needs, the patient's needs, and the physical layout of the room.

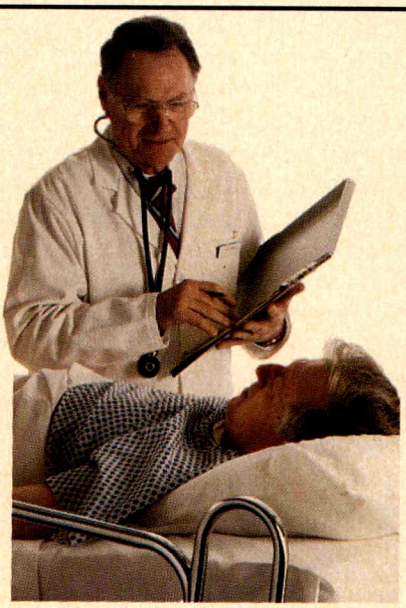
Simplicity itself: intuitive operation, built-in training database, and on-screen "help" and prompts simplify learning for nurses and staff.

Simply put: It's revolutionary. The patient monitoring system that has it all. Sophisticated data management; information reliability; unprecedented versatility with a comprehensive range of interchangeable parameter modules for the ICU/CCU; intuitive operation for ease of use; color displays for enhanced readability; flexibility to customize screens, printed reports, and graphical and tabular trends; bedside recorder for real-time and delayed alarm recording; storage and printout of patient's vital signs over the past 24 or 48 hours; and component modularity for affordability and guaranteed upgradability. Introducing the HP Component Monitoring System.

Now data management is as easy as 1, 2, 3.
Literally. Because our Component Monitoring System does for patient information what the electronic spreadsheet did for business management. Powerful pre-programmed calculations let you see hemodynamic, oxygenation, and



Satellite rack can be mounted in remote locations for maximum convenience and accepts extra parameter modules for additional measurements.



ventilation results on-screen already calculated in tabular format. Now imagine printing that information at the bedside—in any configuration you want, with only the information you want—with all important patient information marked and annotated.

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Instantly. With on-screen access to complete physiological information. Now you can make diagnostic decisions more quickly, easily, and confidently. And, you can even make them at home or in your office with a computer via a modem. You'll also find it easier than ever to check cardiac output and wedge pressures. And another feature you'll appreciate is that every screen, chart, or printout is formatted with a patient ID for accuracy and convenience.

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All in one place. In one system, on one screen. And thanks to component modularity, you can mix and match patient parameter modules, satellite racks, printers, recorders, and displays to tailor that information to your specific needs.

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The new revolution in patient monitoring.

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ARRHYTHMIAS AND CONDUCTION DISTURBANCES

40
Treatment of Ventricular Arrhythmias by United States Cardiologists: a Survey Before the Cardiac Arrhythmia Suppression Trial Results Were Available

Joel Morganroth, J. Thomas Bigger, Jr., and Jeffrey L. Anderson

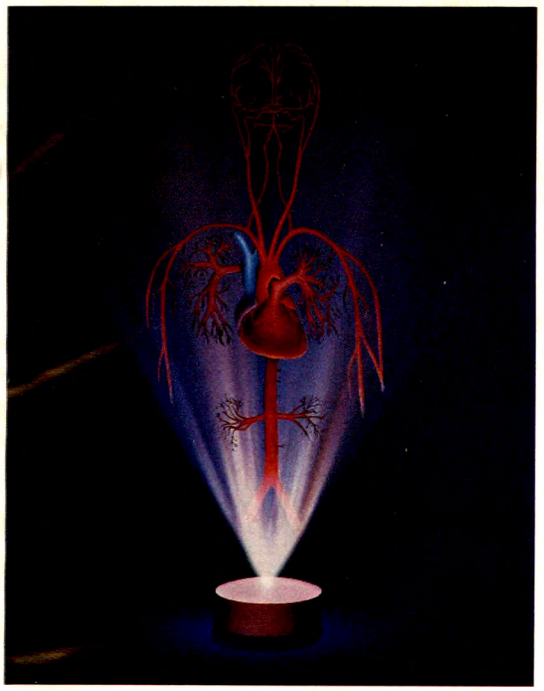
To define the practice habits of United States cardiologists in the treatment of ventricular arrhythmias, a random sample of 1,000 of 12,000 cardiologists was sent a pretested questionnaire and 252 responded. Attitudes about antiarrhythmic drug therapy for the treatment of ventricular arrhythmias were influenced by the presence and severity of cardiac disease, the presence of symptoms and the type of ventricular arrhythmias. In this survey, only 1% of cardiologists treated patients with asymptomatic ventricular premature complexes and no heart disease, but 17% treated such patients if unsustained ventricular tachycardia was present. The treatment rate increased to 38% when coronary artery disease with left ventricular dysfunction was present in patients with asymptomatic ventricular premature complexes. The presence of any cardiac disease and symptomatic ventricular arrhythmias increased the treatment rate to 80 to 100%. Significant confusion exists on the toxicity of antiarrhythmic drugs, use of electrophysiologic testing and in- versus out-of-hospital drug initiation. Approximately 50% of cardiologists treated patients comparable to the Cardiac Arrhythmia Suppression Trial study population although the interim results of the Cardiac Arrhythmia Suppression Trial indicate reconsideration for therapy in such patients.

49
Effect of Basic Drive Cycle Length on the Yield of Ventricular Tachycardia During Programmed Ventricular Stimulation

Joni Summitt, Shimon Rosenheck, William H. Kou, Stephen Schmaltz, Alan H. Kadish, and Fred Morady

In patients in whom sustained, monomorphic ventricular tachycardia (VT) was inducible by programmed stimulation with 1 to 3 ventricular extrastimuli at the right ventricular apex, the yield of VT was 88% when a drive cycle length of 400 ms was used, compared to 64% when the drive cycle length was 600 ms and 32% when the extrastimuli were introduced during sinus rhythm. These results suggest that it is more efficient to begin programmed stimulation using a basic drive cycle length of 400 ms instead of 600 ms or sinus rhythm.

Continued on page A30



New, Once-a-Day

Procardia XL®

(nifedipine) Extended Release

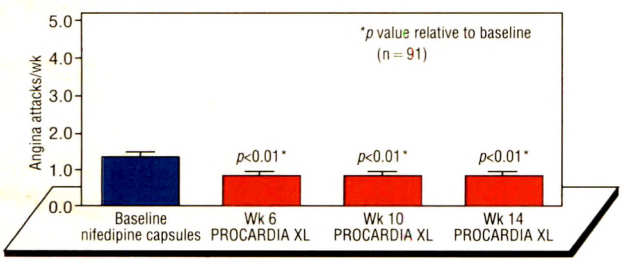
Tablets **30** mg, **60** mg and **90** mg **GITS**

The convenience of a once-a-day calcium channel blocker

Now available for your patients taking PROCARDIA® capsules (nifedipine)

The effectiveness you expect from nifedipine

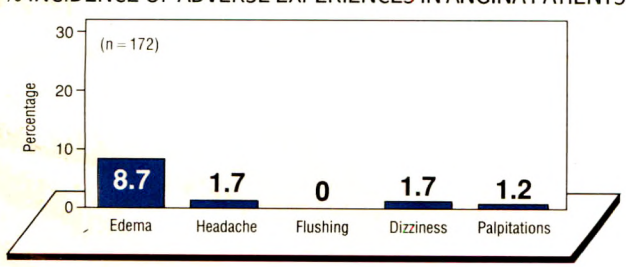
ANGINA FREQUENCY[1]



Fourteen-week, open-label, crossover trial to compare the efficacy and dose equivalency of nifedipine capsules (weeks 1 and 2) vs PROCARDIA XL (weeks 3-14) in 98 patients with chronic stable angina who had been on nifedipine capsules at least one month prior to the study. Patients were switched to the nearest equivalent daily dose over the dose range of 30-150 mg/day. Ninety-five patients were crossed over to receive PROCARDIA XL; 91 of these were evaluated for efficacy. The majority remained on beta blockers and/or nitrates throughout the study. (Reported by Vetrovec GW et al, *Am J Med*, 1987.[1])
Patients were of different races. (Data on file. Medical Department, Pfizer Laboratories, Pfizer Inc.[2])

...With a low incidence of vasodilatory side effects[2]

% INCIDENCE OF ADVERSE EXPERIENCES IN ANGINA PATIENTS[2]



Data obtained from multiple controlled trials of PROCARDIA XL (30-150 mg *q.d.*) in 172 patients with angina. (Data on file. Medical Department, Pfizer Laboratories, Pfizer Inc.[2])

- The most common side effects are peripheral edema, which is not associated with fluid retention, and headache

  In controlled trials of 776 patients with PROCARDIA XL, edema resulted in discontinuation of therapy in 2.7% of patients[2]

...And no significant changes in heart rate[1]

© 1989, Pfizer Inc.

Please see brief summary of prescribing information on the adjacent page.

New, Once-a-Day

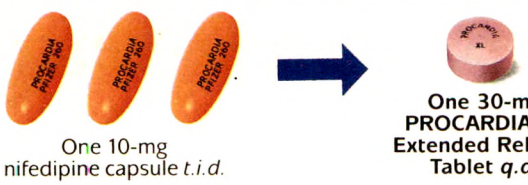
Procardia XL®

(nifedipine) Extended Release

*Tablets **30** mg, **60** mg and **90** mg **GITS***

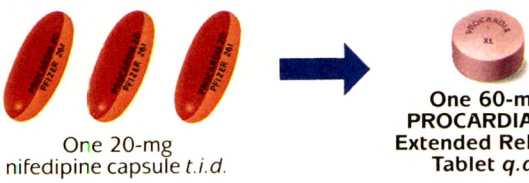
Easy mg-for-mg switch to convenient, once-daily dosing

- Over 90% of angina patients controlled on nifedipine capsules were easily switched to and controlled on PROCARDIA XL Extended Release Tablets at the nearest equivalent total daily dose; others needed dosage adjustment[2]



One 10-mg nifedipine capsule *t.i.d.*

One 30-mg PROCARDIA XL Extended Release Tablet *q.d.*



One 20-mg nifedipine capsule *t.i.d.*

One 60-mg PROCARDIA XL Extended Release Tablet *q.d.*

Switch from Nifedipine Capsules to PROCARDIA XL Extended Release Tablets

Capsules	XL Tablets
30–40 mg/day in divided doses	→ **30 mg once a day**
50–70 mg/day in divided doses	→ **60 mg once a day**
80–100 mg/day in divided doses	→ **90 mg once a day**

- Subsequent dosage adjustments may be necessary and should be initiated as clinically warranted
- The total daily dose can be given with multiple tablets once a day, such as two 60-mg PROCARDIA XL Extended Release Tablets to equal 120 mg total daily dose
- Experience with doses >90 mg in patients with angina is limited; therefore, doses >90 mg should be used with caution and only when clinically warranted

Call 1-800-NOW-RX-XL for additional information on switching to once-a-day PROCARDIA XL Extended Release Tablets.

References:

1. Vetrovec GW, Parker VE, Cole S, et al: Nifedipine gastrointestinal therapeutic system in stable angina pectoris: Results of a multicenter open-label crossover comparison with standard nifedipine. *Am J Med* 1987;83(suppl 6B):24-29.
2. Data on file. Medical Department, Pfizer Laboratories, Pfizer Inc, New York.

Brief Summary
PROCARDIA XL® (nifedipine) Extended Release Tablets For Oral Use

CONTRAINDICATIONS: Known hypersensitivity reaction to nifedipine.

WARNINGS: Excessive Hypotension: Although in most angina patients the hypotensive effect of nifedipine is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving nifedipine together with a beta-blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of nifedipine and a beta blocker, but the possibility that it may occur with nifedipine alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In nifedipine-treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for nifedipine to be washed out of the body prior to surgery.

The following information should be taken into account in those patients who are being treated for hypertension as well as angina:

Increased Angina and/or Myocardial Infarction: Rarely, patients, particularly those who have severe obstructive coronary artery disease, have developed well documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting nifedipine or at the time of dosage increase. The mechanism of this effect is not established.

Beta Blocker Withdrawal: It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning nifedipine. Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of nifedipine treatment will not prevent this occurrence and on occasion has been reported to increase it.

Congestive Heart Failure: Rarely, patients usually receiving a beta blocker, have developed heart failure after beginning nifedipine. Patients with tight aortic stenosis may be at greater risk for such an event, as the unloading effect of nifedipine would be expected to be of less benefit to those patients, owing to their fixed impedance to flow across the aortic valve.

PRECAUTIONS: General—Hypotension: Because nifedipine decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of nifedipine is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See WARNINGS.)

Peripheral Edema: Mild to moderate peripheral edema occurs in a dose dependent manner with an incidence ranging from approximately 10% to about 30% at the highest dose studied (180 mg). It is a localized phenomenon thought to be associated with vasodilation of dependent arterioles and small blood vessels and not due to left ventricular dysfunction or generalized fluid retention. With patients whose angina or hypertension is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Laboratory Tests: Rare, usually transient, but occasionally significant elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted. The relationship to nifedipine therapy is uncertain in most cases, but probable in some. These laboratory abnormalities have rarely been associated with clinical symptoms, however, cholestasis with or without jaundice has been reported. A small (5.4%) increase in mean alkaline phosphatase was noted in patients treated with PROCARDIA XL. This was an isolated finding not associated with clinical symptoms and it rarely resulted in values which fell outside the normal range. Rare instances of allergic hepatitis have been reported. In controlled studies, PROCARDIA XL did not adversely affect serum uric acid, glucose, or cholesterol. Serum potassium was unchanged in patients receiving PROCARDIA XL in the absence of concomitant diuretic therapy, and slightly decreased in patients receiving concomitant diuretics.

Nifedipine, like other calcium channel blockers, decreases platelet aggregation *in vitro*. Limited clinical studies have demonstrated a moderate but statistically significant decrease in platelet aggregation and increase in bleeding time in some nifedipine patients. This is thought to be a function of inhibition of calcium transport across the platelet membrane. No clinical significance for these findings has been demonstrated.

Positive direct Coombs test with/without hemolytic anemia has been reported but a causal relationship between nifedipine administration and positivity of this laboratory test, including hemolysis, could not be determined.

Although nifedipine has been used safely in patients with renal dysfunction and has been reported to exert a beneficial effect in certain cases, rare reversible elevations in BUN and serum creatinine have been reported in patients with pre-existing chronic renal insufficiency. The relationship to nifedipine therapy is uncertain in most cases but probable in some.

Drug Interactions—Beta-adrenergic blocking agents: (See WARNINGS) Experience in over 1400 patients with Procardia® capsules in a noncomparative clinical trial has shown that concomitant administration of nifedipine and beta-blocking agents is usually well tolerated but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension, or exacerbation of angina.

Long Acting Nitrates: Nifedipine may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Digitalis: Administration of nifedipine with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with coronary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing nifedipine to avoid possible over- or under-digitalization.

Coumarin Anticoagulants: There have been rare reports of increased prothrombin time in patients taking coumarin anticoagulants to whom nifedipine was administered. However, the relationship to nifedipine therapy is uncertain.

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak nifedipine plasma levels (80%) and area-under-the-curve (74%), after a one week course of cimetidine at 1000 mg per day and nifedipine at 40 mg per day. Ranitidine produced smaller, non-significant increases. The effect may be mediated by the known inhibition of cimetidine on hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of nifedipine. If nifedipine therapy is initiated in a patient currently receiving cimetidine, cautious titration is advised.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Nifedipine was administered orally to rats, for two years and was not shown to be carcinogenic. When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose. *In vivo* mutagenicity studies were negative.

Pregnancy: Pregnancy Category C. Nifedipine has been shown to be teratogenic in rats when given in doses 30 times the maximum recommended human dose. Nifedipine was embryotoxic (increased fetal resorptions, decreased fetal weight, increased stunted forms, increased fetal deaths; decreased neonatal survival) in rats, mice, and rabbits at doses of from 3 to 10 times the maximum recommended human dose. In pregnant monkeys, doses 2-3 and twice the maximum recommended human dose resulted in small placentas and underdeveloped chorionic villi. In rats, doses three times maximum human dose and higher caused prolongation of pregnancy. There are no adequate and well controlled studies in pregnant women. PROCARDIA XL® (nifedipine) Extended Release Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

ADVERSE EXPERIENCES: Over 1000 patients from both controlled and open trials with PROCARDIA XL Extended Release Tablets in hypertension and angina were included in the evaluation of adverse experiences. All side effects reported during PROCARDIA XL Extended Release Tablet therapy were tabulated independent of their causal relation to medication. The most common side effect reported with PROCARDIA XL was edema which was dose related and ranged in frequency from approximately 10% to about 30% at the highest dose studied (180 mg). Other common adverse experiences reported in placebo-controlled trials include: headache (15.8%, compared to 9.8% placebo incidence), fatigue (5.9%, compared to 4.1% placebo incidence), dizziness (4.1%, compared to 4.5% placebo incidence), constipation (3.3%, compared to 2.3% placebo incidence), and nausea (3.3%, compared to 1.9% placebo incidence). Of these, only edema and headache were more common in PROCARDIA XL patients than placebo patients.

The following adverse reactions occurred with an incidence of less than 3.0%. With the exception of leg cramps, the incidence of these side effects was similar to that of placebo alone: *body as a whole/systemic:* asthenia, flushing, pain; *cardiovascular:* palpitations; *central nervous system:* insomnia, nervousness, paresthesia, somnolence; *dermatologic:* pruritus, rash; *gastrointestinal:* abdominal pain, diarrhea, dry mouth, dyspepsia, flatulence; *musculoskeletal:* arthralgia, leg cramps; *respiratory:* chest pain (nonspecific), dyspnea; *urogenital:* impotence, polyuria.

Other adverse reactions were reported sporadically with an incidence of 1.0% or less. These include: *body as a whole/systemic:* face edema, fever, hot flashes, malaise, periorbital edema, rigors; *cardiovascular:* arrhythmia, hypotension, increased angina, tachycardia, syncope; *central nervous system:* anxiety, ataxia, decreased libido, depression, hypertonia, hypoesthesia, migraine, paroniria, tremor, vertigo; *dermatologic:* alopecia, increased sweating, urticaria, purpura; *gastrointestinal:* eructation, gastroesophageal reflux, gum hyperplasia, melena, vomiting, weight increase; *musculoskeletal:* back pain, gout, myalgias; *respiratory:* coughing, epistaxis, upper respiratory tract infection, respiratory disorder, sinusitis; *special senses:* abnormal lacrimation, abnormal vision, taste perversion, tinnitus; *urogenital/reproductive:* breast pain, dysuria, hematuria, nocturia.

Adverse experiences which occurred in less than 1 in 1000 patients cannot be distinguished from concurrent disease states or medications.

In multiple-dose U.S. and foreign controlled studies with nifedipine capsules in which adverse reactions were reported spontaneously, adverse effects were frequent but generally not serious and rarely required discontinuation of therapy or dosage adjustment. Most were expected consequences of the vasodilator effects of Procardia. Adverse experiences reported in placebo-controlled trials include: dizziness, lightheadedness, and giddiness (27%, compared to 15% placebo incidence); flushing, heat sensation (25%, compared to 8% placebo incidence); headache (23%, compared to 20% placebo incidence); weakness (12%, compared to 10% placebo incidence); nausea, heartburn (11%, compared to 8% placebo incidence); muscle cramps, tremor (8%, compared to 3% placebo incidence); peripheral edema (7%, compared to 1% placebo incidence); nervousness, mood changes (7%, compared to 4% placebo incidence); palpitation (7%, compared to 5% placebo incidence); dyspnea, cough, and wheezing (6%, compared to 3% placebo incidence); and nasal congestion, sore throat (6%, compared to 8% placebo incidence).

There is also a large uncontrolled experience in over 2100 patients in the United States. Most of the patients had vasospastic or resistant angina pectoris, and about half had concomitant treatment with beta-adrenergic blocking agents. The relatively common adverse events were similar in nature to those seen with PROCARDIA XL.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

In a subgroup of over 1000 patients receiving Procardia with concomitant beta blocker therapy, the pattern and incidence of adverse experiences was not different from that of the entire group of Procardia treated patients (See PRECAUTIONS.)

In a subgroup of approximately 250 patients with a diagnosis of congestive heart failure as well as angina, dizziness or lightheadedness, peripheral edema, headache or flushing each occurred in one in eight patients. Hypotension occurred in about one in 20 patients. Syncope occurred in approximately one patient in 250. Myocardial infarction or symptoms of congestive heart failure each occurred in about one patient in 15. Atrial or ventricular dysrhythmias each occurred in about one patient in 150.

More detailed professional information available on request.

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New Insights into Pacemaker Syndrome Gained from Hemodynamic, Humoral and Vascular Responses During Ventriculo-Atrial Pacing

Kenneth A. Ellenbogen, Marc D. Thames, and Pramod K. Mohanty

We studied the hemodynamic and neurohumoral responses to atrial, ventricular and ventriculo-atrial (V-A) pacing at 600 ms (100 beats/min) in 16 patients with a left ventricular ejection fraction >35%. We measured forearm blood flow (ml/min/100 ml), forearm vascular resistance (U), mean arterial pressure (mm Hg), cardiac output (liters/min) and plasma norepinephrine (pg/ml) during each mode of pacing before and after regional α blockade with intraarterial phentolamine. During V-A pacing, cardiac output decreased by 10%, whereas forearm vascular resistance increased from 51 ± 7 to 70 ± 9 U ($p < 0.001$) and plasma norepinephrine increased from 183 ± 27 to 232 ± 27 pg/ml ($p < 0.01$). Phentolamine nearly abolished the increase in forearm vascular resistance in response to V-A pacing (18 ± 4.1 before, to 5.8 ± 1.5 U after, $p < 0.05$). Responses of forearm vascular resistance correlated with changes in systolic arterial pressure. We conclude that ventricular pacing with V-A conduction at 100 to 150 ms increases plasma norepinephrine and forearm vascular resistance, and these responses are mediated by baroreflex-induced sympathoexcitation and by α-adrenergic receptor activation.

SYSTEMIC HYPERTENSION

60

Assessment of Four Ambulatory Blood Pressure Monitors and Measurements by Clinicians Versus Intraarterial Blood Pressure at Rest and During Exercise

William B. White, Per Lund-Johansen, and Per Omvik

We assessed the accuracy of 4 different ambulatory blood pressure (BP) monitors by comparing them to simultaneous intraarterial BP during rest, isometric and dynamic (bicycle) exercise in 48 patients. These differences were then compared to the disparities found between clinicians using a mercury column and intraarterial BP. During rest, 2 monitors (Accutracker II and Colin ABPM 630) showed less disparity than clinicians did with intraarterial BP while the other 2 monitors (Del Mar P-IV and SpaceLabs 90202) showed similar disagreement. Mean BP differences with intraarterial determinations were greater for all monitors and the clinicians during exercise. Again, the Accutracker II and Colin ABPM 630 were found to be similar to the discrepancies observed with clinicians and the Del Mar P-IV showed greater error. The SpaceLabs 90202 had a >80% rate of error codes during exercise.

Continued on page A35

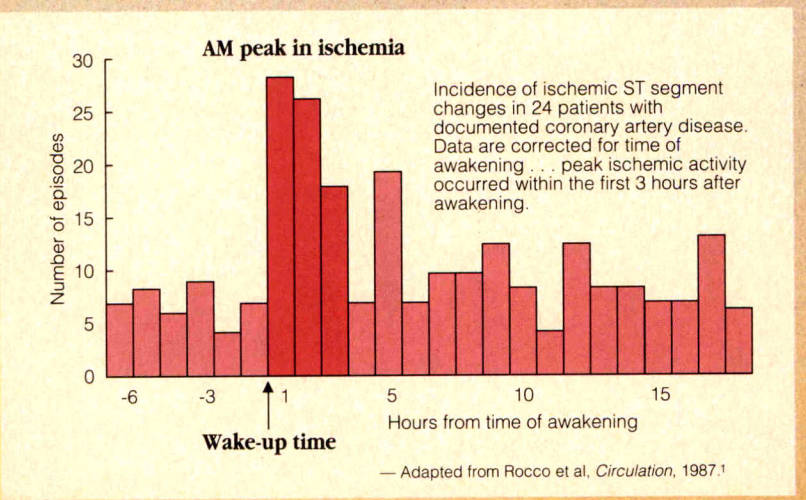


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J-1844

As predictable as the sunrise…

The morning rise in myocardial ischemia[1]



Studies indicate that a similar circadian pattern also exists for:

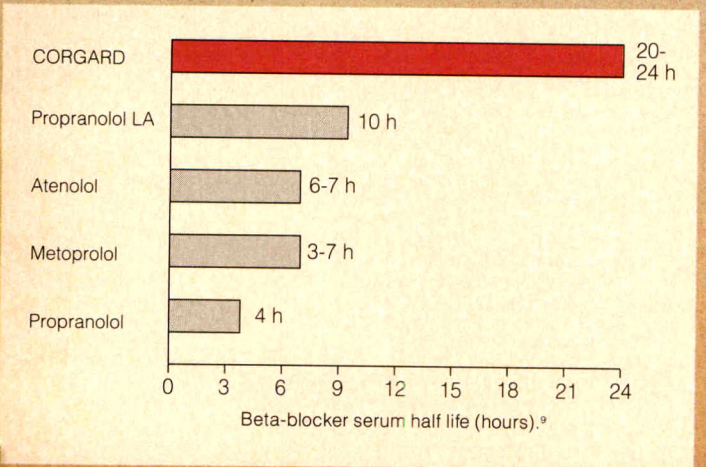
- —Myocardial infarction[2]
- —Sudden cardiac death[3]
- —Ischemic stroke[4]
- —Heart rate[5]
- —Blood pressure[5]
- —Plasma catecholamines[6]
- —Platelet aggregation.[6]

Corgard® (nadolol tablets) is not indicated for treatment or prevention of myocardial infarction, sudden cardiac death, or ischemic stroke.

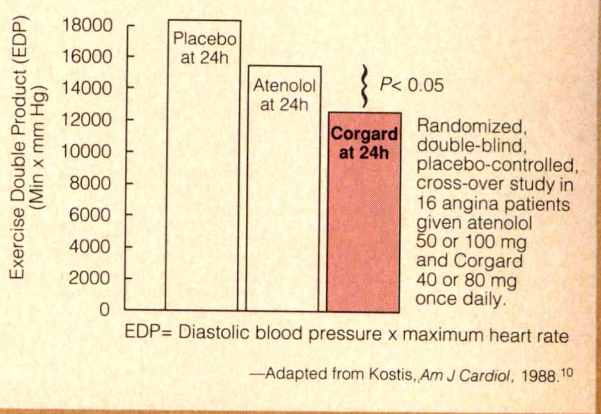
CORGARD

24-hour antianginal protection… throughout the circadian pattern of myocardial ischemia[7]

Corgard: The beta blocker with the longest duration of action[8]… and the longest half life[9]



Corgard: Significantly greater suppression of exercise double product than atenolol at 24 hours[10]



—Adapted from Kostis, *Am J Cardiol*, 1988.[10]

CORGARD®

(nadolol tablets)

On guard, 24 hours a day

Please see brief summary of prescribing information on adjacent page.

CORGARD®
(nadolol tablets)
On guard, 24 hours a day



CORGARD® TABLETS
Nadolol Tablets USP

DESCRIPTION: CORGARD (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal—Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery—Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia—Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis—Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Renal Function—Use nadolol with caution (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients—Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign of impending failure. Advise patients in event of missed doses.

Drug Interactions—Concurrent administration may result in interactions with: Anesthetics, general—exaggeration of the hypotension induced by general anesthetics (see WARNINGS, Major Surgery). Antidiabetic drugs (oral agents and insulin)—hypoglycemia or hyperglycemia; adjust antidiabetic drug dosage accordingly (see WARNINGS, Diabetes and Hypoglycemia). Catecholamine-depleting drugs (e.g., reserpine)—additive effect; monitor closely for hypotension and/or excessive bradycardia.

Carcinogenesis, Mutagenesis, Impairment of Fertility—In 1 to 2 year oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy Category C—In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus. Neonates of mothers who received nadolol at parturition have exhibited bradycardia, hypoglycemia and associated symptoms.

Nursing Mothers—Nadolol is excreted in human milk. Exercise caution when nadolol is administered to a nursing woman.

Pediatric Use—Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular—Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System—**Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory—**Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal—**Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous—** Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision; infrequent reversible alopecia.

The following adverse reactions have been reported in patients taking nadolol and/or other beta-adrenergic blocking agents, but no causal relationship to nadolol has been established. **Central Nervous System—**reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal—**mesenteric arterial thrombosis; ischemic colitis; elevated liver enzymes. **Hematologic—**agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic—**fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous—** pemphigoid rash; hypertensive reaction in patients with pheochromocytoma; sleep disturbances; Peyronie's disease. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia—Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure—Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension—Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm—Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE—For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg qd; may be gradually increased in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 40 or 80 mg qd (doses up to 160 or 240 mg daily may be needed). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg qd; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 40 or 80 mg qd (doses up to 240 or 320 mg daily may be needed).

Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

For full prescribing information consult package insert.

HOW SUPPLIED: In scored tablets containing 20, 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100. The 40 mg, 80 mg, and 120 mg tablets are available in bottles of 1000 tablets. The 20 mg, 40 mg, and 80 mg tablets are also available in Unimatic® unit-dose packs of 100 tablets.
(J4-156)

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References: 1. Rocco MB, Barry J, Campbell S, et al: Circadian variation of transient myocardial ischemia in patients with coronary artery disease. *Circulation* 75:395-400;1987. 2. Muller JE, Stone PH, Turi ZG, et al: Circadian variation in the frequency of onset of acute myocardial infarction. *N Engl J Med* 313:1315-1322;1985. 3. Willich SN, Levy D, Rocco MB, Tofler GH, Stone PH, Muller JE: Circadian variation in the incidence of sudden cardiac death in the Framingham Heart Study population. *Am J Cardiol* 60:801-806;1987. 4. Marler JR, Price TR, Clark GL, et al: Morning increase in onset of ischemic stroke. *Stroke* 20:473-476;1989. 5. Millar-Craig MW, Bishop CN, Raftery EB: Circadian variation of blood-pressure. *Lancet* 1:795-797;1978. 6. Tofler GH, Brezinski D, Schafer AI, et al: Concurrent morning increase in platelet aggregability and the risk of myocardial infarction and sudden cardiac death. *N Engl J Med* 316:1514-1518;1987. 7. Kostis JB, Lacy CR, Krieger SD, et al: Atenolol, nadolol, and pindolol in angina pectoris on effort: effect of pharmacokinetics. *Am Heart J* 108:1131-1136;1984. 8. Vukovich RA, Foley JE, Brown B, et al: Effect of β-blockers on exercise double product (systolic blood pressure × heart rate). *Br J Clin Pharmacol* 7(suppl 2): 167S-172S;1979. 9. *Physicians' Desk Reference®*, ed 43, Medical Economics Company, Inc., Oradell, NJ, 1989, pp. 969, 1037, 1635, 2306, 2308. 10. Kostis JB: Comparison of the duration of action of atenolol and nadolol for treatment of angina pectoris. *Am J Cardiol* 62:1171-1175;1988.

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829-505

Issued: October 1989

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Concurrent Compliance Reduction and Increased Peripheral Resistance in the Manifestation of Isolated Systolic Hypertension

David S. Berger and John K.-J. Li

The hemodynamic mechanisms responsible for the production of isolated systolic hypertension (ISH) were studied with the use of a computer simulation of the modified Windkessel model of the arterial tree. The model parameters, arterial compliance (C), peripheral resistance (Rs) and characteristic impedance (Zo), were derived from experimental aortic pressure and flow data. Aortic flow was then used as the input to the model, allowing us to quantify changes in systolic and diastolic pressures (P_s and P_d) due to changes in the parameters. Graded reductions of C resulted in percent changes in P_s and P_d that would not result in ISH. An increase in Rs of 25% along with a decrease in C of 50 to 75%, however, did result in ISH in the model predictions. We conclude that ISH is usually not the result of decreased compliance alone, but is due to greatly reduced arterial compliance along with increased peripheral resistance.

VALVULAR HEART DISEASE

72

Failure of Balloon Aortic Valvuloplasty to Result in Sustained Clinical Improvement in Patients with Depressed Left Ventricular Function

Charles J. Davidson, J. Kevin Harrison, Mark E. Leithe, Katherine B. Kisslo, and Thomas M. Bashore

This study was designed to determine whether clinical characteristics, including invasive hemodynamic parameters of left ventricular (LV) performance, are predictive of short-term patient outcome. The acute hemodynamic results obtained in patients with overall improved symptoms were compared to those with recurrent symptoms at 3 months. Fifty-three patients (65%) were improved at the 3-month evaluation (group 1), whereas 28 patients (35%) had developed return of symptoms. Compared to patients with improved symptoms, patients with recurrent symptoms demonstrated a lower cardiac output, higher LV end-systolic volume, decreased LV ejection fraction, diminished LV stroke work and decreased LV peak positive dP/dt. The final aortic valve area and change in aortic valve area or ejection fraction did not predict which patients would develop recurrent symptoms. Stepwise logistic regression revealed that LV ejection fraction was the only independent predictor of overall status at 3 months ($p = 0.002$).

Continued on page A36

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Effect of Isometric Exercise on Mitral and Aortic Regurgitation as Assessed by Color Doppler Flow Imaging

Michael G. Spain, Mikel D. Smith, Oi Ling Kwan, and Anthony N. DeMaria

The purpose of this study was to assess the effect of isometric exercise (handgrip) on the severity of valvular regurgitation as measured by color flow Doppler jet areas. Thirty-four patients with 43 regurgitant lesions had color Doppler imaging performed at baseline and during sustained handgrip using a calibrated dynamometer. Regurgitant jet areas were reported as the maximal area of disturbed flow by planimetry. In 20 cases of aortic regurgitation, mean jet area increased from 4.5 to 6.2 cm^2 ($p < 0.0001$) during isometric exercise. For 23 cases of mitral regurgitation the mean jet area increased from 6.2 to 8.2 cm^2 ($p < 0.001$). Thus, color Doppler imaging detected an increase in jet areas during handgrip, suggesting that isometric exercise increased the amount of mitral and aortic regurgitation due to changes in loading conditions.

MISCELLANEOUS

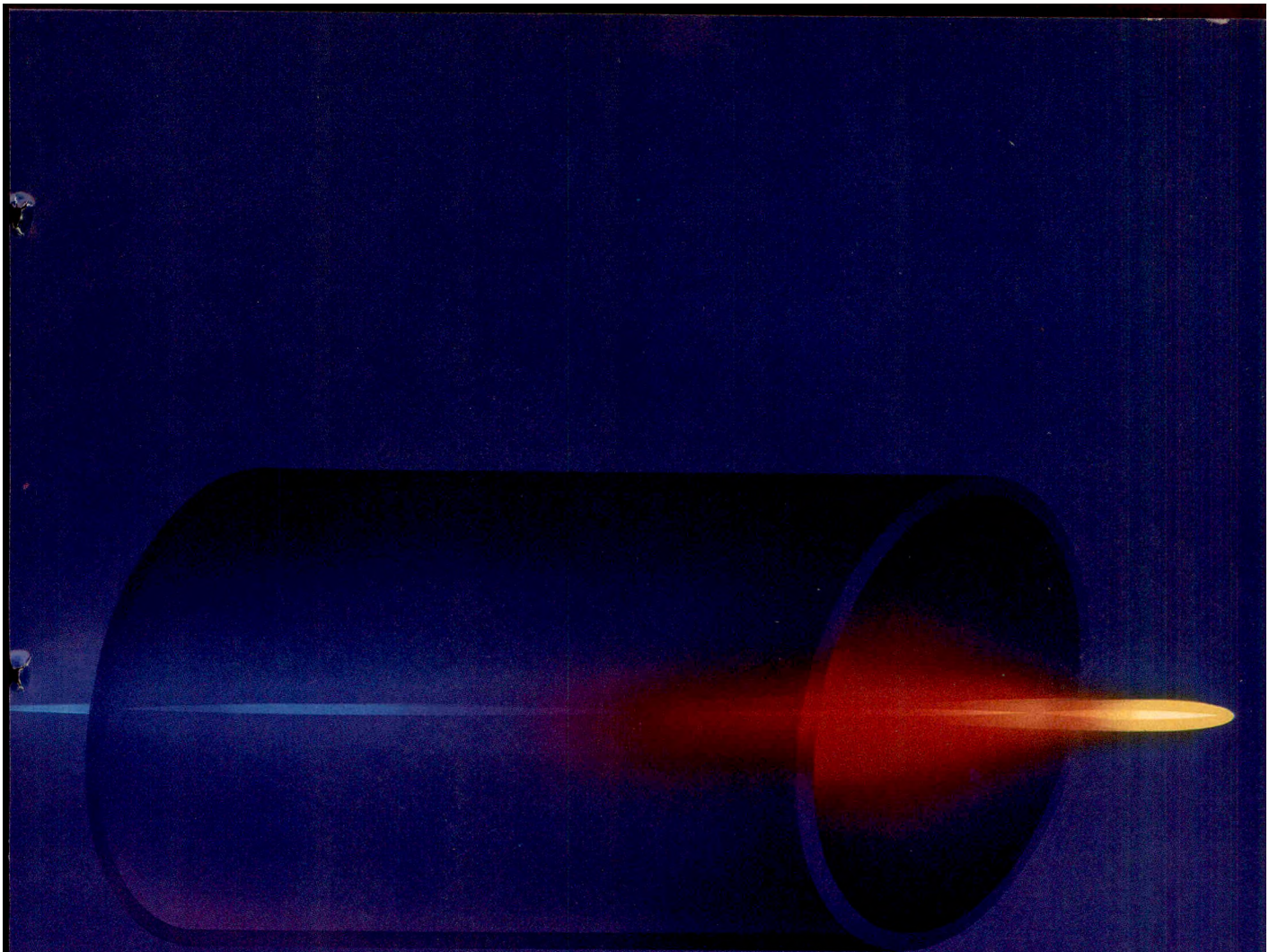
84

Short- and Long-Term Effects of Cigarette Smoking on Heart Rate Variability

Junichiro Hayano, Masami Yamada, Yusaku Sakakibara, Takao Fujinami, Kiyoko Yokoyama, Yosaku Watanabe, and Kazuyuki Takata

To investigate the short- and long-term effects of cigarette smoking on autonomic cardiac regulation, we analyzed the changes in the heart rate spectral components with smoking and the differences in the components between nonsmokers and smokers after an overnight abstinence. The respiratory component, an index of vagal cardiac control, decreased 3 minutes after the start of smoking ($p = 0.0061$), whereas the Mayer wave component (0.04 to 0.15 Hz), which includes sympathetically mediated activity, increased 10 to 17 minutes after the start of smoking ($p = 0.0124$). The respiratory component in the supine position was smaller in the young (≤30 years) heavy smokers (>25 cigarettes/day) than in the nonsmokers or moderate (1 to 24 cigarettes/day) smokers ($p = 0.0078$). Also, postural responses in the components were observed in the nonsmokers but not in the heavy smokers. Our results suggest that smoking causes not only short- but also long-term reduction in vagal cardiac control.

Continued on page A42



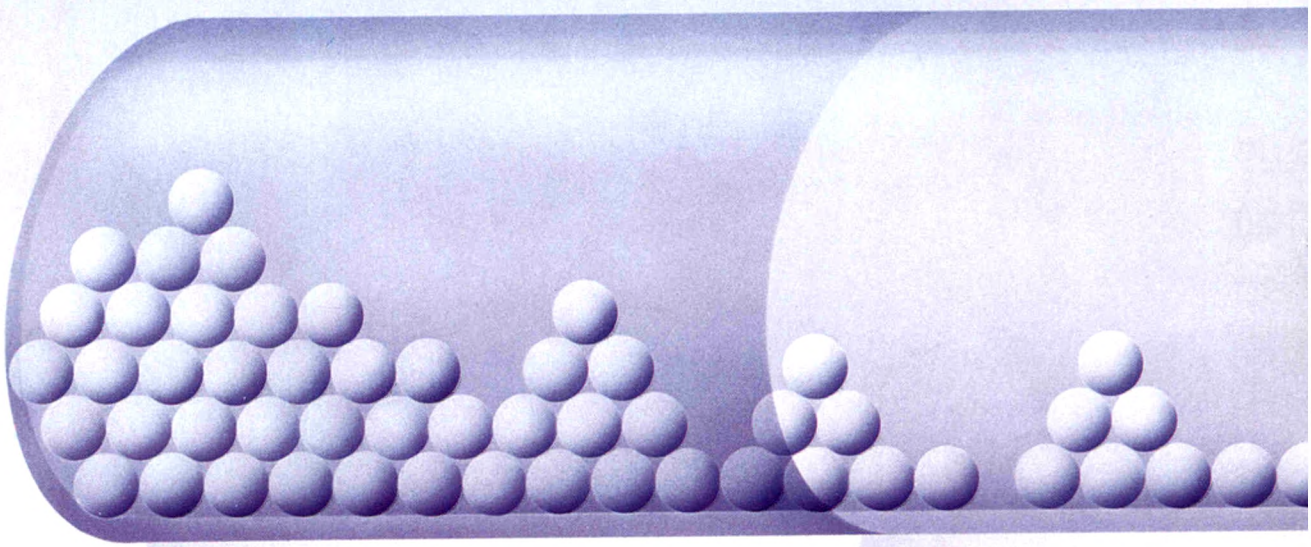
Evidence directly linking elevated cholesterol and CAD made you take a closer look at lipid levels

BUT THERE'S MORE...

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Lorelco is indicated for the reduction of elevated serum cholesterol in patients with primary hypercholesterolemia, as an adjunct to diet.

LOWERING ELEVATED
MAY BE JUST



Lorelco *(probucol)* offers proven long-term cholesterol-lowering efficacy*

- *Reduces total cholesterol by up to 27%*[1,2]
- *Maintains lower levels, as proven over a 12-year period*[3]
- *Provides the assurance of extensive clinical experience*

**The effect of probucol-induced reduction of serum cholesterol or triglyceride levels or reduction of HDL-cholesterol levels on morbidity or mortality due to coronary heart disease has not been established.*

References: 1. *S Afr Med J 1982;62:7-11.* **2.** *Arch Intern Med 1981;141:1428-1432.* **3.** *Data on file, MERRELL DOW PHARMACEUTICALS INC., Cincinnati, Ohio 45242-9553.* **4.** *Am J Cardiol 1988;62:31B-36B.* **5.** *Atherosclerosis 1986;62:209-217.* **6.** *Proc Natl Acad Sci USA 1987;84:5928-5931.* **7.** *J Clin Invest 1986;77:641-644.* **8.** *Proc Natl Acad Sci USA 1987;84:7725-7729.* **9.** *Am J Cardiol 1988;62:6B-12B.* **10.** *Am J Cardiol 1986;57:16H-21H.* **11.** *Am J Cardiol 1988;62:57B-59B.* **12.** *Am J Cardiol 1988;62:66B-72B.* **13.** *Am J Cardiol 1988;62:73B-76B.* **14.** *Am J Cardiol 1988;62:52B-56B.*

Lorelco affects cholesterol in unique ways†

- *Inhibits the oxidative modification of LDL*[4-10]
- *Enhances HDL-mediated reverse cholesterol transport*‡§

†Unique modes of action suggested by rece in vitro studies and human and/or animal in vivo data; clinical significance, however, is yet established.

‡These effects of probucol on LDL- (increase abolic rate) and HDL-cholesterol may be linke observed increased excretion of fecal bile acid final metabolic pathway for elimination of cho from the body. (See Clinical Pharmacology.)

§The probable benefits obtained from LDL-cho reduction must be weighed against the possible of a reduction in HDL-cholesterol when assessing response of each patient receiving treatment wit Lorelco. If satisfactory lipid alteration is not achie the drug should be discontinued. (See Precautions

LEVELS
THE BEGINNING



Lorelco provides important patient compliance benefits

- *Convenient dosage—just one 500 mg tablet b.i.d. with meals*
- *Well tolerated—the most frequent side effect is loose stools, which occurs in about one in ten patients and generally subsides during continued therapy. See Prescribing Information for full discussion of side effects.*
- *Economical—can offer significant cost savings vs most other cholesterol-lowering therapies*

Lorelco is not an innocuous drug and strict attention should be paid to the Indications, Contraindications, Warnings, and Precautions sections of Prescribing Information.

See Prescribing Information appearing on next page.

LORELCO® PROBUCOL 500
500 mg tablets b.i.d. with meals

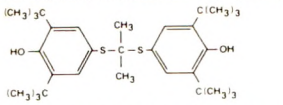
TAKES YOU TO THE NEXT LEVEL OF CHOLESTEROL CONTROL

Merrell Dow U.S.A.

Lorelco® Tablets (probucol)

CAUTION: Federal law prohibits dispensing without prescription.

DESCRIPTION: Lorelco (probucol) film-coated tablets for oral administration contain 250 mg or 500 mg of probucol per tablet. Each tablet also contains as inactive ingredients: corn starch, ethylcellulose, glycerin, hydroxypropyl cellulose, hydroxypropyl methylcellulose 2910, iron oxide, lactose, magnesium stearate, microcrystalline cellulose, polysorbate 80, talc, and titanium dioxide. Lorelco is an agent for the reduction of elevated serum cholesterol. The chemical name is 4,4′-[(1-methylethylidene)bis(thio)]bis[2,6-bis(1,1-dimethylethyl)phenol]. Its chemical structure does not resemble that of any other available cholesterol-lowering agent. It is lipophilic.



CLINICAL PHARMACOLOGY: Lorelco lowers total serum cholesterol and has relatively little effect on serum triglycerides. Patients responding to probucol exhibit a decrease in low-density lipoprotein (LDL) cholesterol. Cholesterol is reduced not only in the LDL fraction, but also in the high-density lipoprotein (HDL) fraction with proportionately greater effect on the high-density portion. Epidemiologic studies have shown that both low HDL-cholesterol and high LDL-cholesterol are independent risk factors for coronary heart disease. The risk of lowering HDL-cholesterol while lowering LDL-cholesterol remains unknown. There is little or no effect reported on very low-density lipoprotein (VLDL).

Studies on the mode of action of Lorelco indicate that it increases the fractional rate of LDL catabolism. This effect may be linked to the observed increased excretion of fecal bile acids, a final metabolic pathway for the elimination of cholesterol from the body. Lorelco also exhibits inhibition of early stages of cholesterol biosynthesis and slight inhibition of absorption of dietary cholesterol. There is no increase in the cyclic precursors of cholesterol, namely desmosterol and 7-dehydrocholesterol. On this basis, it is concluded that Lorelco does not affect the later stages of cholesterol biosynthesis.

Absorption of Lorelco from the gastrointestinal tract is limited and variable. When it is administered with food, peak blood levels are higher and less variable. With continuous administration in a dosage of 500 mg b.i.d., the blood levels of an individual gradually increase over the first three to four months and thereafter remain fairly constant. In 116 patients treated with Lorelco for periods of three months to one year, the mean blood level was 23.6 ± 17.2 mcg/mL (± S.D.) ranging to 78.3 mcg/mL. Levels observed after seven years of treatment in 40 patients yielded an average value of 21.5 ± 16.5 mcg/mL (± S.D.) ranging to 62.0 mcg/mL. In a separate study in eight patients, blood levels averaged 19.0 mcg/mL at the end of 12 months of treatment. Six weeks after cessation of therapy, the average had fallen by 60%. After six months, the average had fallen by 80%.

In December 1984, a National Institutes of Health Consensus Development Conference Panel† concluded that lowering definitely elevated blood cholesterol levels (specifically blood levels of LDL-cholesterol) will reduce the risk of heart attacks due to coronary heart disease. The effect of probucol-induced reduction of serum cholesterol or triglyceride levels, or reduction of HDL-cholesterol levels on morbidity or mortality due to coronary heart disease has not been established.

INDICATIONS AND USAGE: Serious animal toxicity has been encountered with probucol. See WARNINGS and ANIMAL PHARMACOLOGY AND TOXICOLOGY sections. Probucol is not an innocuous drug and strict attention should be paid to the INDICATIONS, CONTRAINDICATIONS, and WARNINGS.

Drug therapy should not be used for the routine treatment of elevated blood lipids for the prevention of coronary heart disease. Dietary therapy specific for the type of hyperlipidemia is the initial treatment of choice. Excess body weight may be an important factor and should be addressed prior to any drug therapy. Physical exercise can be an important ancillary measure. Contributory disease such as hypothyroidism or diabetes mellitus should be looked for and adequately treated. The use of drugs should be considered only when reasonable attempts have been made to obtain satisfactory results with nondrug methods. If the decision ultimately is to use drugs, the patient should be instructed that this does not reduce the importance of adhering to diet.

The selection of patients for cholesterol-lowering drug therapy should take into account other important coronary risk factors such as smoking, hypertension, and diabetes mellitus. Consideration should be given to the efficacy, safety, and compliance factors for each of the cholesterol-lowering drugs prior to selecting the one most appropriate for an individual patient.

Lorelco may be indicated for the reduction of elevated serum cholesterol in patients with primary hypercholesterolemia (Types IIa and IIb hyperlipoproteinemia),[2] whose elevated LDL-cholesterol has not responded adequately to diet, weight reduction, and control of diabetes mellitus. Lorelco may be useful to lower elevated LDL-cholesterol that occurs in those patients with combined hypercholesterolemia and hypertriglyceridemia (Type IIb) due to elevation of both LDL and VLDL, but it is not indicated where hypertriglyceridemia is the abnormality of most concern. After establishing that the elevation in serum total cholesterol represents a primary lipid disorder, it should be determined that patients being considered for treatment with Lorelco have an elevated LDL-cholesterol as the cause for an elevated total serum cholesterol. This may be particularly relevant for patients with elevated triglycerides or with markedly elevated HDL-cholesterol values, where non-LDL fractions may contribute significantly to total cholesterol levels without apparent increase in cardiovascular risk. In most patients, LDL-cholesterol may be estimated according to the following equation:

$$\text{LDL-cholesterol} = \text{Total cholesterol} - [(0.16 \times \text{triglycerides}) + \text{HDL-cholesterol}]$$

When total triglycerides are greater than 400 mg/dL, this equation is less accurate. In such patients, LDL-cholesterol may be obtained by ultracentrifugation.

It is not always possible to predict from the lipoprotein type or other factors which patients will exhibit favorable results. Lipid levels, including HDL-cholesterol, should be periodically assessed.

The effect of probucol-induced reduction of serum cholesterol or triglyceride levels, or reduction of HDL-cholesterol levels on morbidity or mortality due to coronary heart disease has not been established.

CONTRAINDICATIONS: (See also WARNINGS and PRECAUTIONS.) Lorelco is contraindicated in patients who are known to have a hypersensitivity to it. Lorelco is contraindicated in patients with evidence of recent or progressive myocardial damage or findings suggestive of serious ventricular arrhythmias or with unexplained syncope or syncope of cardiovascular origin.

Lorelco is contraindicated in patients with an abnormally long QT interval.

WARNINGS: SERIOUS ANIMAL TOXICITY HAS BEEN ENCOUNTERED WITH PROBUCOL IN RHESUS MONKEYS FED AN ATHEROGENIC DIET AND IN BEAGLE DOGS. (SEE ANIMAL PHARMACOLOGY AND TOXICOLOGY SECTION.)

Prolongation of the QT interval can occur in patients on Lorelco. Serious arrhythmias have been seen in association with an abnormally long QT interval in patients on Lorelco alone and in patients on Lorelco and a concomitant antiarrhythmic drug. The following precautions are deemed prudent:

1. Patients should be advised to adhere to a low cholesterol, low fat diet at the start of treatment with Lorelco and throughout the treatment period.
2. An ECG should be done prior to starting treatment and repeated at appropriate intervals during treatment. If an abnormally long QT interval is observed, the possible benefits and risks should be carefully considered before making a decision to continue Lorelco.

   Lorelco therapy should be discontinued or not started if the QT interval at an observed heart rate on a resting ECG is persistently more than one of the values listed below:

Observed Heart Rate (beats/min)	QT Interval in sec (15% above the upper limit of normal)*	
	Males	Females
40	0.56	0.58
50	0.52	0.53
60	0.49	0.50
70	0.45	0.47
80	0.43	0.44
86	0.42	0.43
92	0.40	0.41
100	0.39	0.40
109	0.37	0.38
120	0.36	0.36
133	0.34	0.35

   *Values calculated from Burch GE, Winsor T. A primer of electrocardiography. Philadelphia, PA: Lea and Febiger; 1958; p. 272 (Table 6).

3. Patients developing unexplained syncope or syncope of cardiovascular origin should have Lorelco therapy discontinued and should have ECG surveillance.
4. Drugs that prolong the QT interval are more likely to be associated with ventricular tachycardia after:
   a. An increase in the dose of the drug.
   b. Addition of a second drug that prolongs the QT interval (including tricyclic antidepressants, class I and III antiarrhythmics, and phenothiazines).
   c. Hypokalemia or hypomagnesemia.
   d. Severe bradycardia due to intrinsic heart disease or drug effects on the atrial rate (beta-blockers) or AV block (digoxin).
   e. Development of recent or acute myocardial infarction, ischemia, or inflammation.

The use of Lorelco in patients receiving any of these drugs should be based on the conclusion that alternate methods of hypocholesterolemic therapy are either ineffective or not tolerated, and the potential benefits of cholesterol lowering outweigh the risk of serious arrhythmia.

The following conditions should be resolved or corrected prior to initiation of therapy with Lorelco:

a. Hypokalemia
b. Hypomagnesemia
c. Severe bradycardia due to intrinsic heart disease or drug effects on the atrial rate (beta-blockers) or AV block (digoxin).
d. Recent or acute myocardial infarction, ischemia, or inflammation.

PRECAUTIONS

General: Before instituting therapy with Lorelco, adequate baseline studies should be performed to determine that the patient has persistently elevated total and LDL-cholesterol levels representing a primary lipid disorder, and that the increased cholesterol is not due to secondary conditions such as hypothyroidism, poorly controlled diabetes mellitus, obstructive liver disease, nephrotic syndrome, or dysproteinemias. Serum lipid levels, including HDL-cholesterol, should be determined after an overnight fast before treatment, during an adequate trial of diet and weight reduction therapy prior to addition of drug therapy, and periodically during combined diet and drug therapy, including assessment during the first several months of drug treatment. A favorable trend in lipid levels should be evident during the first three to four months of administration of Lorelco, and if satisfactory lipid alteration is not achieved, the drug should be discontinued. Lorelco lowers serum total and LDL-cholesterol, and also lowers HDL-cholesterol in most patients with elevated LDL-cholesterol. Epidemiologic studies within hypercholesterolemic populations have shown that serum HDL-cholesterol is an independent, inversely correlated, risk factor for coronary heart disease (see CLINICAL PHARMACOLOGY). Human studies which will attempt to confirm or deny the hypothesis that drug-induced alteration in HDL-cholesterol affects cardiovascular risk are currently under evaluation. It is not known whether Lorelco-induced reduction of serum HDL-cholesterol will affect cardiovascular risk since no long-term, controlled clinical trials of Lorelco for the prevention of coronary heart disease, similar to the LRC-CPPT (see CLINICAL STUDIES), have been performed. The probable benefits obtained from LDL-cholesterol reduction must be weighed against the possible risk of a reduction in HDL-cholesterol when assessing the response of each patient receiving Lorelco treatment. If satisfactory lipid alteration is not achieved, the drug should be discontinued.

Information for Patients: The patient should be instructed to adhere to a prudent diet. Females should be cautioned against becoming pregnant for at least six months after discontinuing Lorelco and should not breast-feed their infants during therapy with Lorelco.

Laboratory Tests: The physician should schedule periodic blood lipid determinations and periodic ECGs. (See WARNINGS.)

Elevations of the serum transaminases (SGOT, SGPT), bilirubin, alkaline phosphatase, creatine phosphokinase, uric acid, blood urea nitrogen, and blood glucose above the normal range were observed on one or more occasions in various patients treated with Lorelco. Most often these were transient and/or could have been related to the patient's clinical state or other modes of therapy. Although the basis for the relationship between Lorelco and these abnormalities is not firm, the possibility that some of these are drug related cannot be excluded. In controlled trials, the incidence of abnormal laboratory values was no higher in the patients treated with Lorelco than in the patients who received placebo. If abnormal laboratory tests persist or worsen, if clinical signs consistent with the abnormal laboratory tests develop, or if systemic manifestations occur, Lorelco should be discontinued.

Drug Interactions: The addition of clofibrate to Lorelco is not recommended, since the lowering effect on mean serum levels of either LDL or total cholesterol is generally not significantly additive and, in some patients, there may be a pronounced lowering of HDL-cholesterol.

Neither oral hypoglycemic agents nor oral anticoagulants alter the effect of Lorelco on serum cholesterol. The dosage of these agents is not usually modified when given with Lorelco.

Monkeys fed a high fat, high cholesterol diet admixed with probucol exhibited serious toxicity. (See WARNINGS and ANIMAL PHARMACOLOGY AND TOXICOLOGY sections.) Prolongation of the QT interval can occur in patients on Lorelco and serious arrhythmias have been seen in association with an abnormally long QT interval in patients on Lorelco. The addition of a second drug that prolongs the QT interval (including tricyclic antidepressants, class I and III antiarrhythmics, and phenothiazines) may increase the risk of serious arrhythmia. (See CONTRAINDICATIONS AND WARNINGS.)

Carcinogenesis, Mutagenesis, Impairment of Fertility

In chronic studies of two years' duration in rats, no toxicity or carcinogenicity was observed. These results are consistent with the lack of any adverse effect on fertility and the negative findings in tests for mutagenic activity in rats.

Pregnancy

Teratogenic Effects

Pregnancy—Category B: Reproduction studies have been performed in rats and rabbits at doses up to 50 times the human dose, and have revealed no evidence of impaired fertility or harm to the fetus due to probucol. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Furthermore, if a patient wishes to become pregnant, it is recommended that the drug be withdrawn and birth control procedures be used for at least six months because of persistence of the drug in the body for prolonged periods. (See CLINICAL PHARMACOLOGY.)

Labor And Delivery: The effect of Lorelco on human labor and delivery is unknown.

Nursing Mothers: It is not known whether this drug is excreted in human milk, but it is likely, since such excretion has been shown in animals. It is recommended that nursing not be undertaken while a patient is on Lorelco.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Gastrointestinal
diarrhea or loose stools, flatulence, abdominal pain, nausea, vomiting, indigestion, gastrointestinal bleeding

Cardiovascular
prolongation of the QT interval on ECG, syncope, ventricular arrhythmias (ventricular tachycardia, torsades de pointes, ventricular fibrillation), sudden death

Neurologic
headache, dizziness, paresthesia, insomnia, tinnitus, peripheral neuritis

Hematologic
eosinophilia, low hemoglobin and/or hematocrit, thrombocytopenia

Dermatologic
rash, pruritus, ecchymosis, petechiae, hyperhidrosis, fetid sweat

Genitourinary
impotency, nocturia

Ophthalmic
conjunctivitis, tearing, blurred vision

Endocrine
enlargement of multinodular goiter

Idiosyncrasies
observed with initiation of therapy and characterized by dizziness, palpitations, syncope, nausea, vomiting and chest pai

Other
diminished sense of taste and smell, anorexia, angioneurotic edema

DRUG ABUSE AND DEPENDENCE: No evidence of abuse potential has been associated with Lorelco, nor is there evidence of psychological or physical dependence in humans.

OVERDOSAGE: There is a single report of a 15-kg, three-year-old, male child who ingested 5 g of probucol. Emesis was induced by ipecac. The child remained well, apart from a brief episode of loose stools and flatulence. No specific information is available on the treatment of overdosage with Lorelco and no specific antidote is available. Probucol is not dialyzable. Treatment is symptomatic and supportive. Probucol has shown no identifiable acute toxicity in mice and rats. In these animals the LD_{50} (oral) is in excess of 5 g/kg of body weight.

DOSAGE AND ADMINISTRATION: For adult use only. The recommended and maximal dose is 1000 mg daily given in two divided doses of 500 mg each (two 250 mg tablets or one 500 mg tablet) with the morning and evening meals.

HOW SUPPLIED: 250 mg round, white, film-coated tablets imprinted with either the DOW diamond trademark over the code number 51 or LORELCO 250. Bottles of 120 (NDC 0068-0051-52)

500 mg capsule-shaped, white, film-coated tablets, marked LORELCO 500. Bottles of 100 (NDC 0068-0053-61)

Keep well closed. Store in a dry place. Avoid excessive heat. Dispense in well-closed light-resistant containers with child resistant closure.

ANIMAL PHARMACOLOGY AND TOXICOLOGY: In rhesus monkeys, administration of probucol in diets containing unusually high amounts of cholesterol and saturated fat resulted in the death of four of eight animals after several weeks. Premonitory syncope was frequently observed and was associated with a pronounced prolongation of the QT intervals (30 to 50% longer than that observed in untreated monkeys). Serum levels of probucol greater than 20 mcg/mL were generally associated with some prolongation in the QT interval in the cholesterol-fed monkey. A 75 msec or greater increase in QT interval from control values was usually seen at 40 mcg/mL and above. Blood levels in humans receiving Lorelco average approximately 20 mcg/mL and not uncommonly reach levels of 40 mcg/mL and higher. Rhesus monkeys fed normal (low fat) chow and receiving probucol three to thirty times the human dose equivalent achieved blood levels only one-third those of many human subjects. No adverse effects were detected in these monkeys over an eight-year period of continuous drug administration.

another study in rhesus monkeys, an atherogenic diet was fed for two years and daily treatment with probucol, separated in time from the atherogenic meal, was carried out during the second year. Serum probucol levels ranged 20 to 50 mcg/mL in five of the monkeys, and less in the remaining animals. Marked prolongation of the QT_c interval in the ECG or syncopal behavior was never observed over the entire one-year treatment period. Regression of gross aortic lesions comparable to that observed in a parallel group of monkeys receiving cholestyramine was seen in animals receiving probucol. It should be emphasized that both HDL-cholesterol and LDL-cholesterol were markedly reduced in this regression study. During the performance of a two-year chronic study involving 32 probucol-treated dogs (beagles), there were 12 fatalities.

Subsequent experiments have indicated that probucol sensitizes the canine myocardium to epinephrine, resulting in ventricular fibrillation in many dogs. Among the animal species in which probucol has been studied, the dog is peculiar with respect to this phenomenon of sudden death due to the sensitization of the myocardium to epinephrine. In contrast to findings in the dog, injections of epinephrine to probucol-treated monkeys did not induce ventricular fibrillation.

In other studies, monkeys were given probucol either before and after, or only after myocardial infarction was induced by coronary artery ligation. In these studies, there was no difference between probucol- and placebo-treated groups with respect to either survival or detailed blind quantitation of myocardial changes (gross and histopathologic).

Probucol has shown no identifiable toxicity in mice and rats. In these animals, the LD_{50} (oral) is in excess of 5 g/kg of body weight. In chronic studies of two years' duration in rats, no toxicity or carcinogenicity was observed.

From studies in rats, dogs, and monkeys, it is known that probucol accumulates slowly in adipose tissue. Approximately 90% of probucol administered orally is unabsorbed. For that which is absorbed, the biliary tract is the major pathway for clearance from the body and very little is excreted by way of the kidneys.

Myocardial injury was produced in various groups of rats by one of the following procedures: aortic coarctation, coronary ligation, or cobalt or isoproterenol injection. After probucol administration, no deleterious effects related to treatment occurred as measured by survival and microscopic examination of myocardial damage.

Probucol was administered to minipigs beginning ten days before ligation of coronary artery and continued for 60 days after surgery. Challenge with epinephrine at the end of 60 days failed to induce ventricular fibrillation in any of the coronary-ligated probucol-treated minipigs.

CLINICAL STUDIES: In a multicenter, randomized, double-blind study, the LRC-CPPT,[3] hypercholesterolemic patients treated with an oral bile acid sequestrant (cholestyramine) and a cholesterol-lowering diet experienced average total and LDL-cholesterol reductions greater than those obtained in the placebo group treated with diet alone. The cumulative seven-year incidence of the primary end point—combined incidence of definite CHD death and/or definite nonfatal myocardial infarction—was 7% in the cholestyramine group and 8.6% in the placebo group. This was a 19% reduction in risk (P less than 0.05, single tail test) of the primary end point reflecting a 24% reduction in definite CHD death and a 19% reduction in nonfatal myocardial infarction.

The subjects included in the study were middle-aged men (35-59 years old) with serum cholesterol levels at least 265 mg/dL and no previous history of heart disease. It is not clear to what extent these findings can be extrapolated to other segments of the hypercholesterolemic population not studied.

The bile acid sequestrant, cholestyramine, was used in the above trial. Caution should be exercised in extrapolating these results to Lorelco since it differs from cholestyramine with regard to its mode of action, spectrum of cholesterol-lowering potency, effect on HDL-cholesterol, and possible toxicity. The effect of probucol-induced reduction of serum cholesterol levels on morbidity or mortality due to coronary heart disease has not been established.

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Product Information as of June, 1988

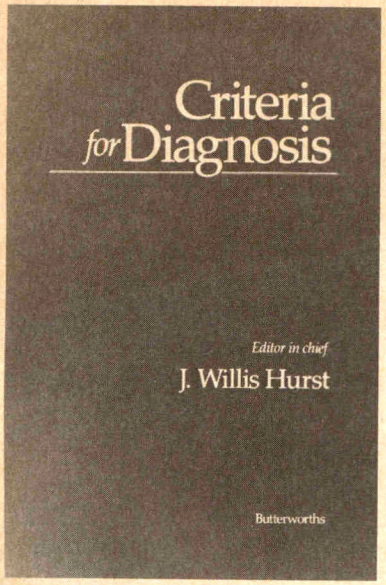
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Pressor Effect of Inhaled Ergotamine in Orthostatic Hypotension

Italo Biaggioni, Deborah Zygmunt, Virginia Haile, and David Robertson

Because venous pooling contributes significantly to the orthostatic hypotension seen in autonomic failure, the venoconstrictive properties of ergotamine offer theoretical advantage in the treatment of this disorder. However, the low and erratic bioavailability of oral preparations has hindered the use of ergotamine. We report the potent pressor effects of inhaled ergotamine tartrate (1 puff, 0.36 mg) compared to placebo in 8 patients with severe autonomic failure. Ergotamine significantly increased systolic (29 ± 5 mm Hg) and diastolic (13 ± 1 mm Hg) blood pressures in the seated position compared to placebo (-9 ± 5 and -2 ± 3 mm Hg, respectively). Upright blood pressures 2 hours after administration were significantly greater with ergotamine ($119 \pm 8/69 \pm 5$ mm Hg) versus placebo ($82 \pm 9/55 \pm 6$ mm Hg, $p < 0.05$). Inhaled ergotamine may provide an effective and practical therapy for disabling orthostatic hypotension.

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Aerobic Exercise Reduces Levels of Cardiovascular and Sympathoadrenal Responses to Mental Stress in Subjects Without Prior Evidence of Myocardial Ischemia

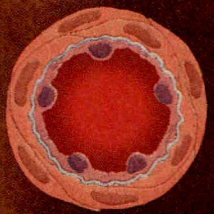
James A. Blumenthal, Mats Fredrikson, Cynthia M. Kuhn, Ross L. Ulmer, Margaret Walsh-Riddle, and Mark Appelbaum

Thirty-seven healthy men were randomly assigned to an aerobic exercise training group or to a strength and flexibility training group. The aerobic exercise consisted of walking and jogging at an intensity of $\geq 70\%$ maximal heart rate reserve for 1 hour 3 times/week. The strength and flexibility exercises consisted of circuit Nautilus training at least twice a week. Before beginning the 3-month exercise programs, subjects completed a physiologic and behavioral assessment, including graded exercise treadmill testing and a mental stress procedure in which subjects performed mental arithmetic while cardiovascular and neuroendocrine responses were monitored. After 12 weeks, subjects in the aerobic group achieved a 14% improvement in peak oxygen consumption, whereas the strength training group experienced only a 3% increase. During the mental stress

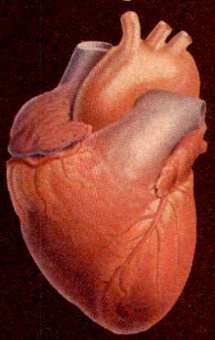
Continued on page A48

THE INSIDE STORY

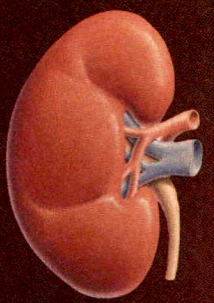
Effective peripheral vasodilation[1]



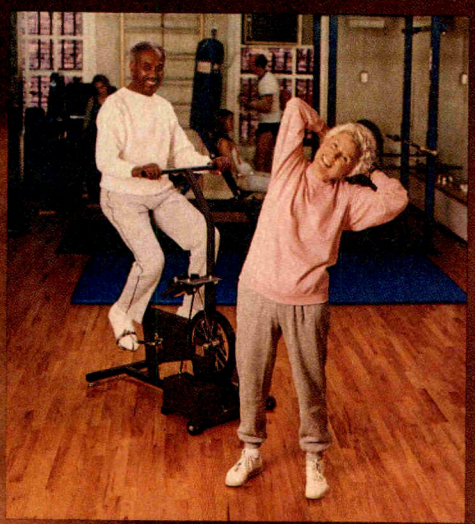
Undiminished cardiac output[2]



Undiminished renal function[3-5]



THE OUTSIDE STORY
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TRANDATE Tablets are contraindicated in bronchial asthma, overt cardiac failure, greater-than-first-degree heart block, cardiogenic shock, and severe bradycardia.

Please see references and Brief Summary of Prescribing Information on adjacent page.

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References: 1. Lund-Johansen P: Short- and long-term (six-year) hemodynamic effects of labetalol in essential hypertension. *Am J Med* 1983;75(suppl 4A):24-31. **2.** Koch G: Haemodynamic adaptation at rest and during exercise to long-term antihypertensive treatment with combined alpha- and beta-adrenoreceptor blockade by labetalol. *Br Heart J* 1979;41(2):192-198. **3.** Wallin JD: Antihypertensives and their impact on renal function. *Am J Med* 1983;75(suppl 4A):103-108. **4.** Pedersen EB, Larsen JS: Effect of propranolol and labetalol on renal haemodynamics at rest and during exercise in essential hypertension. *Postgrad Med J* 1980;56(suppl 2):27-32. **5.** Malini PL, Strocchi E, Negroni S, et al: Renal haemodynamics after chronic treatment with labetalol and propranolol. *Br J Clin Pharmacol* 1982;13(suppl 1):123S-126S.

Trandate® Tablets **BRIEF SUMMARY**
(labetalol hydrochloride)

The following is a brief summary only. Before prescribing, see complete prescribing information in Trandate® Tablets product labeling.

CONTRAINDICATIONS: Trandate® Tablets are contraindicated in bronchial asthma, overt cardiac failure, greater-than-first-degree heart block, cardiogenic shock, and severe bradycardia (see WARNINGS).

WARNINGS: Hepatic Injury: Severe hepatocellular injury, confirmed by rechallenge in at least one case, occurs rarely with labetalol therapy. The hepatic injury is usually reversible, but hepatic necrosis and death have been reported. Injury has occurred after both short- and long-term treatment and may be slowly progressive despite minimal symptomatology. Appropriate laboratory testing should be done at the first symptom/sign of liver dysfunction (eg, pruritus, dark urine, persistent anorexia, jaundice, right upper quadrant tenderness, or unexplained "flu-like" symptoms). If the patient has laboratory evidence of liver injury or jaundice, labetalol should be stopped and not restarted.

Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure. Beta-blockade carries a potential hazard of further depressing myocardial contractility and precipitating more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, labetalol HCl can be used with caution in patients with a history of heart failure who are well compensated. Congestive heart failure has been observed in patients receiving labetalol HCl. Labetalol HCl does not abolish the inotropic action of digitalis on heart muscle.

In Patients Without a History of Cardiac Failure: In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response should be observed closely. If cardiac failure continues despite adequate digitalization and diuretic, Trandate® therapy should be withdrawn (gradually, if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal: Angina pectoris has not been reported upon labetalol HCl discontinuation. However, hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered Trandate, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Trandate administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Trandate therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (eg, Chronic Bronchitis and Emphysema): Patients with bronchospastic disease should, in general, not receive beta-blockers. Trandate may be used with caution, however, in patients who do not respond to, or cannot tolerate, other antihypertensive agents. It is prudent, if Trandate is used, to use the smallest effective dose, so that inhibition of endogenous or exogenous beta-agonists is minimized.

Pheochromocytoma: Labetalol HCl has been shown to be effective in lowering blood pressure and relieving symptoms in patients with pheochromocytoma. However, paradoxical hypertensive responses have been reported in a few patients with this tumor; therefore, use caution when administering labetalol HCl to patients with pheochromocytoma.

Diabetes Mellitus and Hypoglycemia: Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (eg, tachycardia) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia; it may therefore be necessary to adjust the dose of antidiabetic drugs.

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy before major surgery is controversial. Protracted severe hypotension and difficulty in restarting or maintaining a heartbeat have been reported with beta-blockers. The effect of labetalol HCl's alpha-adrenergic activity has not been evaluated in this setting.

A synergism between labetalol HCl and halothane anesthesia has been shown (see PRECAUTIONS: Drug Interactions).

PRECAUTIONS: General: ***Impaired Hepatic Function:*** Trandate® Tablets should be used with caution in patients with impaired hepatic function since metabolism of the drug may be diminished.

Jaundice or Hepatic Dysfunction: (see WARNINGS).

Information for Patients: As with all drugs with beta-blocking activity, certain advice to patients being treated with labetalol HCl is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. While no incidence of the abrupt withdrawal phenomenon (exacerbation of angina pectoris) has been reported with labetalol HCl, dosing with Trandate Tablets should not be interrupted or discontinued without a physician's advice. Patients being treated with Trandate Tablets should consult a physician at any signs or symptoms of impending cardiac failure or hepatic dysfunction (see WARNINGS). Also, transient scalp tingling may occur, usually when treatment with Trandate Tablets is initiated (see ADVERSE REACTIONS).

Laboratory Tests: As with any new drug given over prolonged periods, laboratory parameters should be observed over regular intervals. In patients with concomitant illnesses, such as impaired renal function, appropriate tests should be done to monitor these conditions.

Drug Interactions: In one survey, 2.3% of patients taking labetalol HCl in combination with tricyclic antidepressants experienced tremor as compared to 0.7% reported to occur with labetalol HCl alone. The contribution of each of the treatments to this adverse reaction is unknown, but the possibility of a drug interaction cannot be excluded.

Drugs possessing beta-blocking properties can blunt the bronchodilator effect of beta-receptor agonist drugs in patients with bronchospasm; therefore, doses greater than the normal antiasthmatic dose of beta-agonist bronchodilator drugs may be required.

Cimetidine has been shown to increase the bioavailability of labetalol HCl. Since this could be explained either by enhanced absorption or by an alteration of hepatic metabolism of labetalol HCl, special care should be used in establishing the dose required for blood pressure control in such patients.

Synergism has been shown between halothane anesthesia and intravenously administered labetalol HCl. During controlled hypotensive anesthesia using labetalol HCl in association with halothane, high concentrations (3% or above) of halothane should not be used because the degree of hypotension will be increased and because of the possibility of a large reduction in cardiac output and an increase in central venous pressure. The anesthesiologist should be informed when a patient is receiving labetalol HCl.

Labetalol HCl blunts the reflex tachycardia produced by nitroglycerin without preventing its hypotensive effect. If labetalol HCl is used with nitroglycerin in patients with angina pectoris, additional antihypertensive effects may occur.

Trandate® (labetalol hydrochloride) Tablets

Drug/Laboratory Test Interactions: The presence of labetalol metabolites in the urine may result in falsely elevated levels of urinary catecholamines, metanephrine, normetanephrine, and vanillylmandelic acid when measured by fluorimetric or photometric methods. In screening patients suspected of having a pheochromocytoma and being treated with labetalol HCl, a specific method, such as a high performance liquid chromatographic assay with solid phase extraction (eg, *J Chromatogr* 385: 241,1987) should be employed in determining levels of catecholamines.

Labetalol HCl has also been reported to produce a false-positive test for amphetamine when screening urine for the presence of drugs using the commercially available assay methods Toxi-Lab A® (thin-layer chromatographic assay) and Emit-d.a.u.® (radioenzymatic assay). When patients being treated with labetalol have a positive urine test for amphetamine using these techniques, confirmation should be made by using more specific methods, such as a gas chromatographic-mass spectrometer technique.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term oral dosing studies with labetalol HCl for 18 months in mice and for two years in rats showed no evidence of carcinogenesis. Studies with labetalol HCl using dominant lethal assays in rats and mice and exposing microorganisms according to modified Ames tests showed no evidence of mutagenesis.

Pregnancy: ***Teratogenic Effects: Pregnancy Category C:*** Teratogenic studies were performed with labetalol in rats and rabbits at oral doses up to approximately six and four times the maximum recommended human dose (MRHD), respectively. No reproducible evidence of fetal malformations was observed. Increased fetal resorptions were seen in both species at doses approximating the MRHD. A teratology study performed with labetalol in rabbits at intravenous doses up to 1.7 times the MRHD revealed no evidence of drug-related harm to the fetus. There are no adequate and well-controlled studies in pregnant women. Labetalol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Transient hypotension, bradycardia, and hypoglycemia have been rarely observed in infants of mothers who were treated with labetalol HCl for hypertension during pregnancy. Oral administration of labetalol to rats during late gestation through weaning at doses of two to four times the MRHD caused a decrease in neonatal survival.

Labor and Delivery: Labetalol HCl given to pregnant women with hypertension did not appear to affect the usual course of labor and delivery.

Nursing Mothers: Small amounts of labetalol (approximately 0.004% of the maternal dose) are excreted in human milk. Caution should be exercised when Trandate Tablets are administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects are mild and transient and occur early in the course of treatment. In controlled clinical trials of three to four months' duration, discontinuation of Trandate® Tablets due to one or more adverse effects was required in 7% of all patients. In these same trials, beta-blocker control agents led to discontinuation in 8% to 10% of patients, and a centrally acting alpha-agonist led to discontinuation in 30% of patients.

The following adverse reactions were derived from multicenter, controlled clinical trials over treatment periods of three and four months. The rates, which ranged from less than 1% to 5% except as otherwise noted, are based on adverse reactions considered probably drug-related by the investigator. If all reports are considered, the rates are somewhat higher (eg, dizziness, 20%; nausea, 14%; fatigue, 11%).

Body as a Whole: Fatigue, asthenia, headache. ***Gastrointestinal:*** Nausea (6%), vomiting, dyspepsia, diarrhea, taste distortion. ***Central and Peripheral Nervous Systems:*** Dizziness (11%), paresthesia, drowsiness. ***Autonomic Nervous System:*** Nasal stuffiness, ejaculation failure, impotence, increased sweating. ***Cardiovascular:*** Edema, postural hypotension. ***Respiratory:*** Dyspnea. ***Skin:*** Rash. ***Special Senses:*** Vision abnormality, vertigo.

The adverse effects were reported spontaneously and are representative of the incidence of adverse effects that may be observed in a properly selected hypertensive patient population, ie, a group excluding patients with bronchospastic disease, overt congestive heart failure, or other contraindications to beta-blocker therapy.

Clinical trials also included studies utilizing daily doses up to 2,400 mg in more severely hypertensive patients. The US therapeutic trials data base for adverse reactions that are clearly or possibly dose-related shows that the following side effects increased with increasing dose: dizziness, fatigue, nausea, vomiting, dyspepsia, paresthesia, nasal stuffiness, ejaculation failure, impotence, and edema.

In addition, a number of other less common adverse events have been reported:

Body as a Whole: Fever. ***Cardiovascular:*** Postural hypotension, including, rarely, syncope. ***Central and Peripheral Nervous Systems:*** Paresthesia, most frequently described as scalp tingling. In most cases, it was mild and transient and usually occurred at the beginning of treatment. ***Collagen Disorders:*** Systemic lupus erythematosus, positive antinuclear factor. ***Eyes:*** Dry eyes. ***Immunological System:*** Antimitochondrial antibodies. ***Liver and Biliary System:*** Hepatic necrosis, hepatitis, cholestatic jaundice, elevated liver function tests. ***Musculoskeletal System:*** Muscle cramps, toxic myopathy. ***Respiratory System:*** Bronchospasm. ***Skin and Appendages:*** Rashes of various types, such as generalized maculopapular, lichenoid, urticarial, bullous lichen planus, psoriaform, and facial erythema; Peyronie's disease; reversible alopecia. ***Urinary System:*** Difficulty in micturition, including acute urinary bladder retention.

Following approval for marketing in the United Kingdom, a monitored release survey involving approximately 6,800 patients was conducted for further safety and efficacy evaluation of this product. Results of this survey indicate that the type, severity, and incidence of adverse effects were comparable to those cited above.

Potential Adverse Effects: In addition, other adverse effects not listed above have been reported with other beta-adrenergic blocking agents. ***Central Nervous System:*** Reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on psychometrics. ***Cardiovascular:*** Intensification of A-V block (see CONTRAINDICATIONS). ***Allergic:*** Fever combined with aching and sore throat, laryngospasm, respiratory distress. ***Hematologic:*** Agranulocytosis, thrombocytopenic or nonthrombocytopenic purpura. ***Gastrointestinal:*** Mesenteric artery thrombosis, ischemic colitis. The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with labetalol HCl.

Clinical Laboratory Tests: There have been reversible increases of serum transaminases in 4% of patients treated with labetalol HCl and tested and, more rarely, reversible increases in blood urea.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: DOSAGE MUST BE INDIVIDUALIZED. The recommended *initial* dosage is 100 mg *twice* daily whether used alone or added to a diuretic regimen. After two or three days, using standing blood pressure as an indicator, dosage may be titrated in increments of 100 mg bid every two or three days. The usual *maintenance* dosage of labetalol HCl is between 200 and 400 mg *twice* daily. Before use, see complete prescribing information for dosage details.

April 1989

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TRN647 Printed in USA August 198

The American Journal of Cardiology

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testing, the subjects in the aerobic group experienced a greater reduction in heart rate, diastolic blood pressure and rate pressure product, and tended to secrete less epinephrine and recover faster from the stress than subjects who completed the strength training program. These findings suggest that aerobic exercise reduces levels of cardiovascular and sympathoadrenal responses during and after mental stress.

CARDIOVASCULAR PHARMACOLOGY

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Effects of Nifedipine on the Venodilatory Response to Nitroglycerin
Joseph A. Gascho and William P. Apollo

The purpose of this study was to determine if the venodilatory effect of nitroglycerin was altered by pretreatment with nifedipine. Fifteen healthy male subjects were studied. The venodilatory effect of nitroglycerin in the setting of pretreatment with placebo was compared to the venodilatory effect of nitroglycerin in the setting of pretreatment with nifedipine. VV[30], a measure of the venodilatory effect of nitroglycerin, increased by 0.72 ± 0.52 cc/100 cc arm after nitroglycerin in subjects pretreated with placebo compared to 0.70 ± 0.33 cc/100 cc arm in subjects pretreated with nifedipine. Nifedipine does not appear to alter the venodilatory response to nitroglycerin.

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Clinical and Regulatory Implications of the Cardiac Arrhythmia Suppression Trial
Craig M. Pratt, D. Craig Brater, Frank E. Harrell, Jr., Peter R. Kowey, Carl V. Leier, David T. Lowenthal, Franz Messerli, Milton Packer, Edward L.C. Pritchett, and Jeremy N. Ruskin

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Cardiac Transplant Hypertension
Randall C. Starling and Robert J. Cody

Continued on page A50

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CARDIZEM® TABLETS

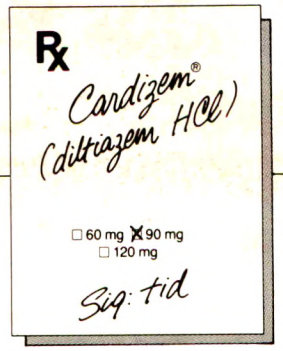
diltiazem HCl/Marion



CARDIZEM® (diltiazem HCl) is indicated in the treatment of angina pectoris due to coronary artery spasm and in the management of chronic stable angina (classic effort-associated angina) in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents.

Please see brief summary of prescribing information on next page.

CAZAA659
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Usual maintenance dosage:
180 to 360 mg/day

CARDIZEM® TABLETS
diltiazem HCl/Marion

MAKING THE DIFFERENCE IN ANGINA



60 mg 90 mg 120 mg

BRIEF SUMMARY

CARDIZEM®
(diltiazem HCl) Tablets

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission.

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1,243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in most cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any agents known to affect cardiac contractility and/or conduction. (See WARNINGS.)

Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of CARDIZEM (diltiazem hydrochloride) concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis: Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or underdigitalization. (See WARNINGS.)

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences as well as their frequency of presentation are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%). In addition, the following events were reported infrequently (less than 1%):

Cardiovascular: Angina, arrhythmia, AV block (first degree), AV block (second or third degree—see conduction warning), bradycardia, congestive heart failure, flushing, hypotension, palpitations, syncope.

Nervous System: Amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor.

Gastrointestinal: Anorexia, constipation, diarrhea, dysgeusia, dyspepsia, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH (see hepatic warnings), vomiting, weight increase.

Dermatologic: Petechiae, pruritus, photosensitivity, urticaria.

Other: Amblyopia, CPK elevation, dyspnea, epistaxis, eye irritation, hyperglycemia, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties.

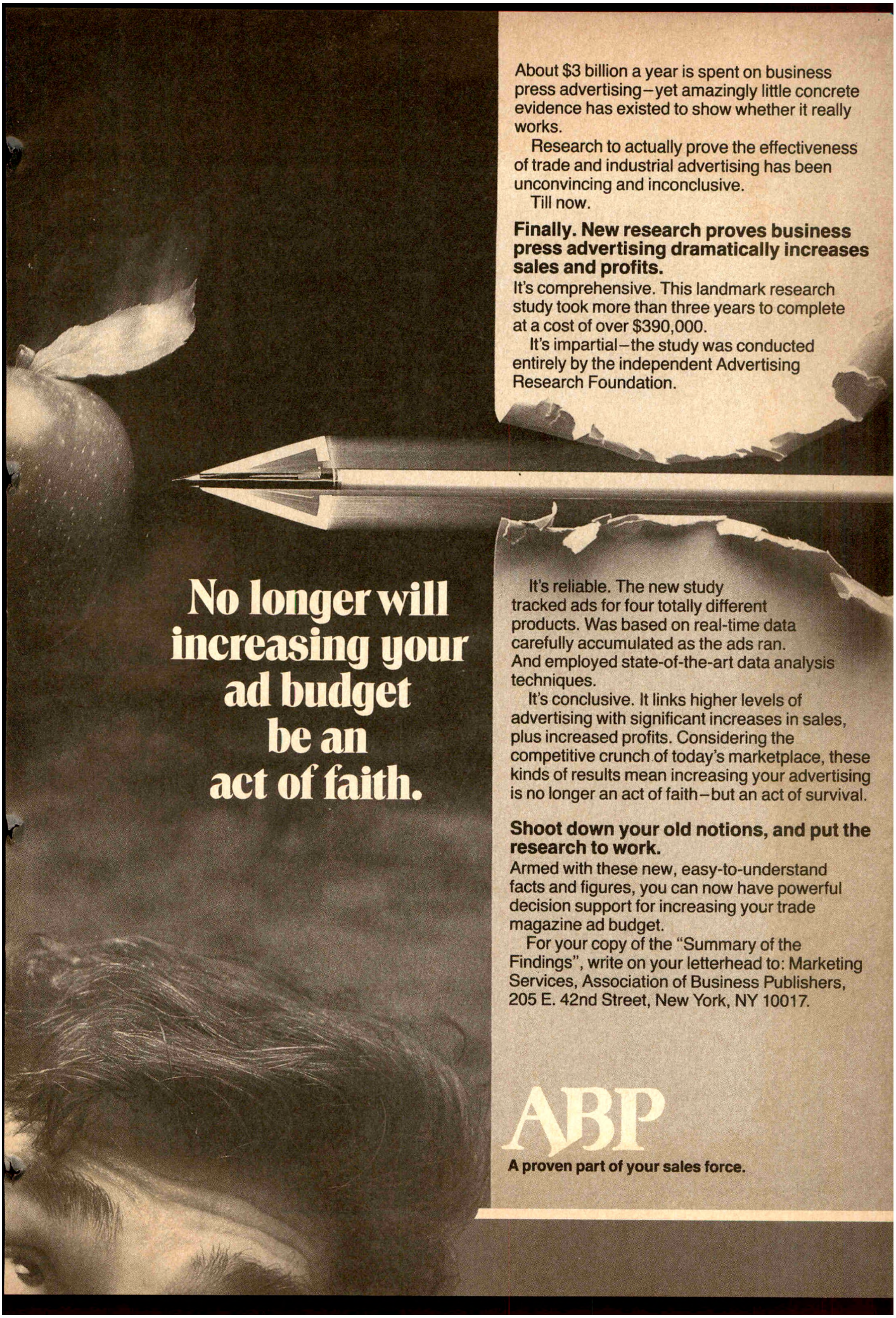
The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, gingival hyperplasia, erythema multiforme, and leukopenia. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.

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William C. Roberts

INSTRUCTIONS TO AUTHORS on page A77

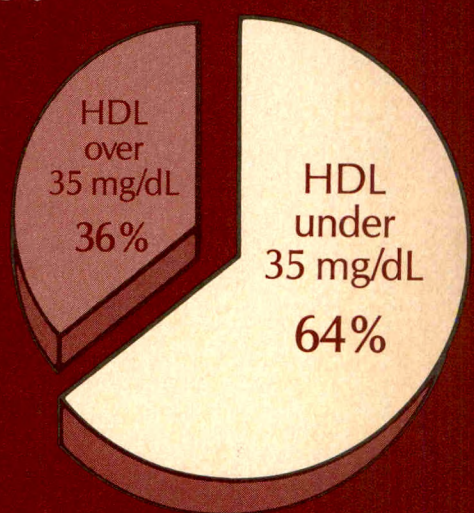
240 TOTAL

<35 HDL

What's a common denominator of most heart attack victims?

Mixed hyperlipidemias—elevated cholesterol *and* triglycerides—are common among heart attack victims,[1] and nearly two thirds of people who developed myocardial infarction in the PROCAM Trial had a low (<35 mg/dL) baseline level of HDL cholesterol.[2]

HEART ATTACK PATIENTS (PROCAM TRIAL)[2]



LOPID raised low HDL 25%

—in patients whose baseline HDL was below 35 mg/dL in the landmark Helsinki Heart Study (HHS).[3]

Reduced heart attack incidence* up to 62%

—in these HHS patients and 45% in HHS patients whose baseline HDL was below the median (46.4 mg/dL). Incidence of serious coronary events was similar for LOPID and placebo subgroups with baseline HDL above the median (46.4 mg/dL).[3]

A powerful case for LOPID®



BID

(*gemfibrozil*) 600-mg Tablets

RAISES HDL...DRAMATICALLY REDUCES HEART ATTACK

LOPID is indicated for reducing the risk of coronary heart disease (CHD) in Type IIb patients with low HDL, in addition to elevated LDL and triglycerides, and who have had an inadequate response to weight loss, diet, exercise, and other pharmacologic agents such as bile acid sequestrants and nicotinic acid.

*Defined as a combination of definite coronary death and/or definite myocardial infarction.

References: 1. Goldstein JL, Hazzard WR, Schrott HG, Bierman EL, Motulsky AG. Hyperlipidemia in coronary heart disease. I. Lipid levels in 500 survivors of myocardial infarction. *J Clin Invest*. 1973;52:1533-1543. **2.** Assmann G, Schulte H. *PROCAM-Trial: Prospective Cardiovascular Münster Trial*. Zürich: Panscientia Verlag; 1986:8-9. **3.** Data on file, Medical Affairs Dept, Parke-Davis.

Please see adjacent page of this advertisement for warnings, contraindications, and brief summary of prescribing information.

PARKE-DAVIS

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Lopid® (Gemfibrozil Capsules and Tablets)

Before prescribing, please see full prescribing information.
A Brief Summary follows.

CONTRAINDICATIONS. 1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.

2. Preexisting gallbladder disease (See WARNINGS).

3. Hypersensitivity to gemfibrozil.

WARNINGS. 1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization (WHO), 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant, 29%, higher total mortality in the clofibrate-treated than in a comparable placebo-treated control group. The excess mortality was due to a 33% increase in noncardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

During the Helsinki Heart Study and in the 1½ year follow-up period since the trial was completed, mortality from any cause was 59 (2.9%) in the Lopid group and 55 (2.7%) in the placebo group. Mortality from any cause during the double-blind portion of the study was 44 deaths in the Lopid group and 43 in the placebo group. Because of the more limited size of the Helsinki Heart Study, this result is not statistically-significantly different from the 29% excess mortality seen in the clofibrate group in the separate WHO study. Noncoronary heart disease related mortality showed a 58% greater trend in the Lopid group (43 vs 27 patients in the placebo group, p=0.056).

In the Helsinki Heart Study, the incidence of total malignancies discovered during the trial and in the 1½ years since the trial was completed was 39 in the Lopid group and 29 in the placebo group (difference not statistically significant). This includes 5 basal cell carcinomas in the Lopid group and none in the placebo group (p=0.06; historical data predicted an expected 4.7 cases in the placebo group). GI malignancies and deaths from malignancies were not statistically different between Lopid and placebo subgroups. Follow-up of the Helsinki Heart Study participants will provide further information on cause-specific mortality and cancer morbidity.

LOPID® Lopid BID
(gemfibrozil) 600-mg Tablets
RAISES HDL...DRAMATICALLY
REDUCES HEART ATTACK

2. A gallstone prevalence substudy of 450 Helsinki Heart Study participants showed a trend toward a greater prevalence of gallstones during the study within the Lopid treatment group (7.5% vs 4.9% for the placebo group, a 55% excess for the gemfibrozil group). A trend toward a greater incidence of gallbladder surgery was observed for the Lopid group (17 vs 11 subjects, a 54% excess). This result did not differ statistically from the increased incidence of cholecystectomy observed in the WHO study in the group treated with clofibrate. Both clofibrate and gemfibrozil may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Lopid therapy should be discontinued if gallstones are found.

3. Since a reduction of mortality from coronary artery disease has not been demonstrated and because liver and interstitial cell testicular tumors were increased in rats, Lopid should be administered only to those patients described in the INDICATIONS AND USAGE section. If a significant serum lipid response is not obtained, Lopid should be discontinued.

4. Concomitant Anticoagulants—Caution should be exercised when anticoagulants are given in conjunction with Lopid. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

5. Concomitant therapy with Lopid and Mevacor® (lovastatin) has been associated with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure (See Drug Interactions). The use of fibrates alone, including Lopid, may occasionally be associated with myositis. Patients receiving Lopid and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myositis, including serum creatine kinase level determination. If myositis is suspected or diagnosed, Lopid therapy should be withdrawn.

6. Cataracts—Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of male rats treated with gemfibrozil at 10 times the human dose.

PRECAUTIONS. 1. **Initial Therapy**—Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal. Before instituting Lopid therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities.

2. **Continued Therapy**—Periodic determination of serum lipids should be obtained, and the drug withdrawn if lipid response is inadequate after 3 months of therapy.

3. **Drug Interactions**—(A) **Lovastatin:** Rhabdomyolysis has occurred with combined gemfibrozil and lovastatin therapy. It may be seen as early as 3 weeks after initiation of combined therapy or after several months. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. There is no assurance that periodic monitoring of creatine kinase will prevent the occurrence of severe myopathy and kidney damage.

(B) **Anticoagulants:** CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

4. **Carcinogenesis, Mutagenesis, Impairment of Fertility**—Long-term studies have been conducted in rats and mice at one and ten times the human dose. The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant (p=0.1). In high dose female rats, there was a significant increase in the combined incidence of benign, and malignant liver neoplasms. In male and female mice, there were no statistically significant differences

Lopid® (Gemfibrozil Capsules and Tablets)

from controls in the incidence of liver tumors, but the doses tested were lower than those shown to be carcinogenic with other fibrates.

Male rats had a dose-related and statistically significant increase of benign Leydig cell tumors at 1 and 10 times the human dose.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following Lopid administration to the male rat. An adequate study to test for peroxisome proliferation has not been done in humans but changes in peroxisome morphology have been observed. Peroxisome proliferation has been shown to occur in humans with either of two other drugs of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Administration of approximately three or ten times the human dose to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to the offspring.

5. **Pregnancy Category B**—Reproduction studies have been performed in the rat at doses 3 and 9 times the human dose, and in the rabbit at 2 and 6.7 times the human dose. These studies have revealed no evidence of impaired fertility in females or harm to the fetus due to Lopid. Minor fetotoxicity was manifested by reduced birth rates observed at the high dose levels. No significant malformations were found among almost 400 offspring from 36 litters of rats and 100 fetuses from 22 litters of rabbits.

There are no studies in pregnant women. In view of the fact that Lopid is tumorigenic in male and female rats, the use of Lopid in pregnancy should be reserved for those patients where the benefit clearly outweighs the possible risk to the patient or fetus.

6. **Nursing Mothers**—Because of the potential for tumorigenicity shown for gemfibrozil in rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

7. **Hematologic Changes**—Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of Lopid therapy. However, these levels stabilize during long-term administration. Rarely, severe anemia, leukopenia, thrombocytopenia, and bone marrow hypoplasia have been reported. Therefore, periodic blood counts are recommended during the first 12 months of Lopid administration.

8. **Liver Function**—Abnormal liver function tests have been observed occasionally during Lopid administration, including elevations of AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase. These are usually reversible when Lopid is discontinued. Therefore periodic liver function studies are recommended and Lopid therapy should be terminated if abnormalities persist.

9. **Use in Children**—Safety and efficacy in children have not been established.

ADVERSE REACTIONS. In the double-blind controlled phase of the Helsinki Heart Study, 2046 patients received Lopid for up to 5 years. In that study, the following adverse reactions were statistically more frequent in subjects in the Lopid group (placebo incidence in parentheses): gastrointestinal reactions, 34.2% (23.8%); dyspepsia, 19.6% (11.9%); abdominal pain, 9.8% (5.6%); acute appendicitis (histologically confirmed in most cases where data are available), 1.2% (0.6%); atrial fibrillation, 0.7% (0.1%).

Adverse events reported by more than 1% of subjects, but without a significant difference between groups (placebo incidence in parentheses) were: diarrhea, 7.2% (6.5%); fatigue, 3.8% (3.5%); nausea/vomiting, 2.5% (2.1%); eczema, 1.9% (1.2%); rash, 1.7% (1.3%); vertigo, 1.5% (1.3%); constipation, 1.4% (1.3%); headache, 1.2% (1.1%).

Gallbladder surgery was performed in 0.9% of Lopid and 0.5% of placebo subjects, a 64% excess, which is not statistically different from the excess of gallbladder surgery observed in the clofibrate compared to the placebo group of the WHO study.

Nervous system and special senses adverse reactions were more common in the Lopid group. These included hypesthesia, paresthesias, and taste perversion. Other adverse reactions that were more common among Lopid treatment group subjects but where a causal relationship was not established include cataracts, peripheral vascular disease, and intracerebral hemorrhage.

From other studies it seems probable that Lopid is causally related to the occurrence of **musculoskeletal symptoms** (See WARNINGS), and to **abnormal liver function tests** and **hematologic changes** (See PRECAUTIONS).

Reports of viral and bacterial infections (common cold, cough, urinary tract infections) were more common in gemfibrozil-treated patients in other controlled clinical trials of 805 patients.

Additional adverse reactions that have been reported for gemfibrozil are listed below by system. These are categorized according to whether a causal relationship to treatment with Lopid is probable or not established:

CAUSAL RELATIONSHIP PROBABLE: *Gastrointestinal:* cholestatic jaundice; *Central Nervous System:* dizziness, somnolence, paresthesia, peripheral neuritis, decreased libido, depression, headache; *Eye:* blurred vision; *Genitourinary:* impotence; *Musculoskeletal:* myopathy, myasthenia, myalgia, painful extremities, arthralgia, synovitis, rhabdomyolysis (see WARNINGS and Drug Interactions under PRECAUTIONS); *Clinical Laboratory:* increased creatine phosphokinase, increased bilirubin, increased liver transaminases (AST [SGOT], ALT [SGPT]), increased alkaline phosphatase; *Hematopoietic:* anemia, leukopenia, bone marrow hypoplasia, eosinophilia; *Immunologic:* angioedema, laryngeal edema, urticaria; *Integumentary:* exfoliative dermatitis, rash, dermatitis, pruritus.

CAUSAL RELATIONSHIP NOT ESTABLISHED: *General:* weight loss; *Cardiac:* extrasystoles; *Gastrointestinal:* pancreatitis, hepatoma, colitis; *Central Nervous System:* confusion, convulsions, syncope; *Eye:* retinal edema; *Genitourinary:* decreased male fertility; *Clinical Laboratory:* positive antinuclear antibody; *Hematopoietic:* thrombocytopenia; *Immunologic:* anaphylaxis, Lupus-like syndrome, vasculitis; *Integumentary:* alopecia.

DOSAGE AND ADMINISTRATION. The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal.

MANAGEMENT OF OVERDOSE. While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

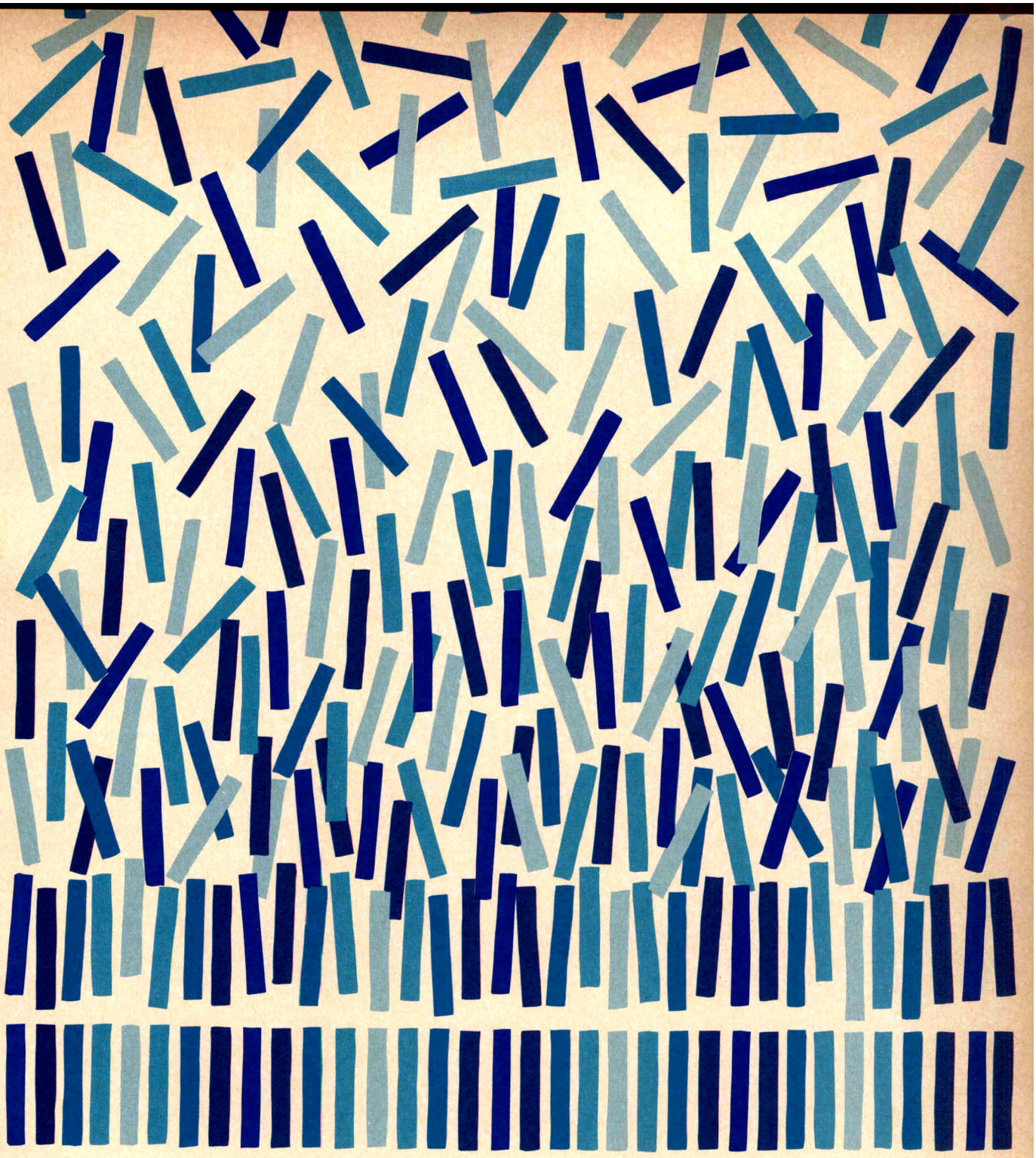
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Caution—Federal law prohibits dispensing without prescription.

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Morris Plains, NJ 07950 USA

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PD-56-JA-5932-A-1(12-89)



Available February, 1990

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propafenone HCl

from Knoll Pharmaceuticals

Knoll Pharmaceuticals
A Unit of BASF K&F Corporation
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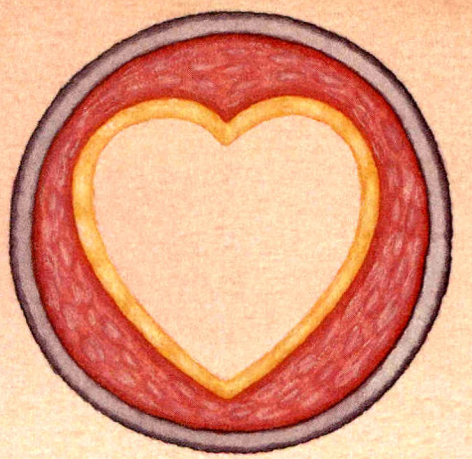
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Kindhearted



LOZOL® (indapamide)

No significant increases in cholesterol in most patients*

In long-term clinical trials, Lozol has demonstrated little or no effect on serum cholesterol levels.[1-3]

Minimal impact on potassium†

95% of patients showed no clinical hypokalemia in a long-term trial.[2]

ONE A DAY LOZOL® INDAPAMIDE 2.5mg

The diuretic that doesn't compromise cholesterol

*Lozol is not a cholesterol-lowering agent, nor has it been shown to reduce existing atherosclerotic plaque.
†Because of the diuretic effects of Lozol, changes in certain electrolytes can occur. Determination of serum electrolytes should therefore be performed.

Brief Summary

DESCRIPTION: Lozol® (indapamide) is an oral antihypertensive/diuretic.

INDICATIONS AND USAGE: Lozol is indicated for the treatment of hypertension, alone or in combination with other antihypertensive drugs.

Lozol is also indicated for the treatment of salt and fluid retention associated with congestive heart failure.

Usage in Pregnancy: (see PRECAUTIONS).

CONTRAINDICATIONS: Anuria. Known hypersensitivity to indapamide or to other sulfonamide-derived drugs.

WARNINGS: Hypokalemia occurs commonly with diuretics, and electrolyte monitoring is essential, particularly in patients who would be at increased risk from hypokalemia, such as those with cardiac arrhythmias or who are receiving concomitant cardiac glycosides.

In general, diuretics should not be given concomitantly with lithium because they reduce its renal clearance and add a high risk of lithium toxicity. Read prescribing information for lithium preparations before use of such concomitant therapy.

PRECAUTIONS: General

1. *Hypokalemia and Other Fluid and Electrolyte Imbalances:* Periodic determinations of serum electrolytes should be performed at appropriate intervals. In addition, patients should be observed for clinical signs of fluid or electrolyte imbalance, such as hyponatremia, hypochloremic alkalosis, or hypokalemia. Warning signs include dry mouth, thirst, weakness, fatigue, lethargy, drowsiness, restlessness, muscle pains or cramps, hypotension, oliguria, tachycardia, and gastrointestinal disturbance. Electrolyte determinations are particularly important in patients who are vomiting excessively or receiving parenteral fluids, in patients subject to electrolyte imbalance (including those with heart failure, kidney disease, and cirrhosis), and in patients on a salt-restricted diet.

The risk of hypokalemia secondary to diuresis and natriuresis is increased when larger doses are used, when the diuresis is brisk, when severe cirrhosis is present and during concomitant use of corticosteroids or ACTH. Interference with adequate oral intake of electrolytes will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis, such as increased ventricular irritability.

Dilutional hyponatremia may occur in edematous patients; the appropriate treatment is restriction of water rather than administration of salt, except in rare instances when the hyponatremia is life threatening. However, in actual salt depletion, appropriate replacement is the treatment of choice. Any chloride deficit that may occur during treatment is generally mild and usually does not require specific treatment except in extraordinary circumstances as in liver or renal disease.

2. *Hyperuricemia and Gout:* Serum concentrations of uric acid increased by an average of 1.0 mg/100 mL in patients treated with indapamide, and frank gout may be precipitated in certain patients receiving indapamide (see ADVERSE REACTIONS below). Serum concentrations of uric acid should therefore be monitored periodically during treatment.

3. *Renal Impairment:* Indapamide, like the thiazides, should be used with caution in patients with severe renal disease, as reduced plasma volume may exacerbate or precipitate azotemia. If progressive renal impairment is observed in a patient receiving indapamide, withholding or discontinuing diuretic therapy should be considered. Renal function tests should be performed periodically during treatment with indapamide.

4. *Impaired Hepatic Function:* Indapamide, like the thiazides, should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

5. *Glucose Tolerance:* Latent diabetes may become manifest and insulin requirements in diabetic patients may be altered during thiazide administration. Serum concentrations of glucose should be monitored routinely during treatment with Lozol.

6. *Calcium Excretion:* Calcium excretion is decreased by diuretics pharmacologically related to indapamide. In long-term studies of hypertensive patients; however, serum concentrations of calcium increased only slightly with indapamide. Prolonged treatment with drugs pharmacologically related to indapamide may in rare instances be associated with hypercalcemia and hypophosphatemia secondary to physiologic changes in the parathyroid gland; however, the common complications of hyperparathyroidism, such as renal lithiasis, bone resorption, and peptic ulcer, have not been seen. Treatment should be discontinued before tests for parathyroid function are performed. Like the thiazides, indapamide may decrease serum PBI levels without signs of thyroid disturbance.

7. *Interaction With Systemic Lupus Erythematosus:* Thiazides have exacerbated or activated systemic lupus erythematosus and this possibility should be considered with indapamide as well.

DRUG INTERACTIONS: 1. *Other Antihypertensives:* Lozol (indapamide) may add to or potentiate the action of other antihypertensive drugs. In limited controlled trials that compared the effect of indapamide combined with other antihypertensive drugs with the effect of the other drugs administered alone, there was no notable change in the nature or frequency of adverse reactions associated with the combined therapy.

2. *Lithium:* See WARNINGS.

3. *Post-Sympathectomy Patient:* The antihypertensive effect of the drug may be enhanced in the post-sympathectomized patient.

4. *Norepinephrine:* Indapamide, like the thiazides, may decrease arterial responsiveness to norepinephrine, but this diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Both mouse and rat lifetime carcinogenicity studies were conducted. There was no significant difference in the incidence of tumors between the indapamide-treated animals and the control groups.

Pregnancy: Teratogenic Effects: Pregnancy Category B. Reproduction studies have been performed in rats, mice and rabbits at doses up to 6,250 times the therapeutic human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Lozol. Postnatal development in rats and mice was unaffected by pretreatment of parent animals during gestation. There are however, no adequate and well-controlled studies in pregnant women. Moreover, diuretics are known to cross the placental barrier and appear in cord blood. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. There may be hazards associated with this use such as fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in the adult.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because most drugs are excreted in human milk, if use of this drug is deemed essential, the patient should stop nursing.

ADVERSE REACTIONS: Most adverse effects have been mild and transient. In long-term controlled clinical studies, cumulative adverse reactions = 5% are: headache, dizziness, fatigue, weakness, loss of energy, lethargy, tiredness, or malaise, muscle cramps or spasm, or numbness of the extremities, nervousness, tension, anxiety, irritability, or agitation. Cumulative adverse reactions ~ 5% are: lightheadedness, drowsiness, vertigo, insomnia, depression, blurred vision, constipation, nausea, vomiting, diarrhea, gastric irritation, abdominal pain or cramps, anorexia, orthostatic hypotension, premature ventricular contractions, irregular heart beat, palpitations, frequency of urination, nocturia, polyuria, rash, hives, pruritus, vasculitis, impotence or reduced libido, rhinorrhea, flushing, hyperuricemia, hyperglycemia, hyponatremia, hypochloremia, increase in serum urea nitrogen (BUN) or creatinine, glycosuria, weight loss, dry mouth, tingling of extremities.

Clinical hypokalemia (i.e., lowered serum potassium concentration with concomitant clinical signs or symptoms) occurred in 3% and 7% of the patients given indapamide 2.5 mg and 5.0 mg, respectively. In a long-term study of both doses (157 patients given indapamide), potassium supplementation was given to 12% of patients on indapamide 2.5 mg and 27% of patients on indapamide 5.0 mg.

Other adverse reactions reported with antihypertensive/diuretics are jaundice (intrahepatic cholestatic jaundice), sialadenitis, xanthopsia, photosensitivity, purpura, necrotizing angiitis, fever, respiratory distress (including pneumonitis), and anaphylactic reactions; also, agranulocytosis, leukopenia, thrombocytopenia, and aplastic anemia. These reactions should be considered as possible occurrences with clinical usage of LOZOL.

HOW SUPPLIED: Lozol (indapamide), White, round film-coated tablets of 2.5 mg in bottles of 100 (NDC 0075-0082-00); 1,000 (NDC 0075-0082-99); and in unit-dose blister packs, boxes of 100 (10 x 10 strips) (NDC 0075-0082-62).

CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription.

Keep tightly closed. Store at room temperature; avoid excessive heat. Dispense in tight containers as defined in USP.

See product circular for full prescribing information. Revised: November 1988 (AS)

References: 1. Meyer-Sabellek W, Gotzen R, Heitz J, et al: Serum lipoprotein levels during long-term treatment of hypertension with indapamide. *Hypertension* 1985;7(suppl 2):170-174. **2.** Beling S, Vukovich RA, Neiss ES, et al: Long-term experience with indapamide. *Am Heart J* 1983;106:258-262. **3.** Scalabrino A, Galeone F, Giuntoli F, et al: Clinical investigation on long-term effects of indapamide in patients with essential hypertension. *Curr Ther Res* 1984;35:17-22.

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The American Journal of Cardiology

JANUARY 1, 1990, VOL. 65, NO. 1

Dyslipidemias with Desirable Plasma Total Cholesterol Levels and Angiographically Demonstrated Coronary Artery Disease

Michael Miller, MD, Lucy A. Mead, ScM, Peter O. Kwiterovich, Jr., MD, and Thomas A. Pearson, MD, PhD

The National Cholesterol Education Program treatment guidelines define a plasma total cholesterol of <200 mg/dl as "desirable" and recommend no further evaluation of plasma lipid or lipoprotein levels in patients with coronary artery disease (CAD). To determine the prevalence of dyslipidemias in the presence of coexistent CAD and total cholesterol ≤200 mg/dl, a retrospective case-control study of 1,000 patients who underwent diagnostic coronary angiography was performed. Of 351 patients with total cholesterol ≤200 mg/dl, 76% of the men (244) and 44% of the women (107) had angiographically demonstrated CAD. In men with CAD and total cholesterol ≤200 mg/dl, there was a significantly greater prevalence of low levels of high density lipoprotein (HDL) cholesterol (≤35 mg/dl), age >50 years, systemic hypertension and diabetes mellitus compared to non-CAD control subjects. In women with CAD and total cholesterol ≤200 mg/dl, HDL cholesterol ≤45 mg/dl and diabetes mellitus were also significantly prevalent. Multiple logistic regression analyses revealed that HDL cholesterol, hypertension and age in men and very low density lipoprotein cholesterol in women were significantly associated with CAD after adjustment for other risk factors. These results suggest that a complete lipid and lipoprotein analysis be obtained in all patients with CAD, irrespective of the plasma (or serum) total cholesterol level.

(Am J Cardiol 1990;65:1–5)

From the Lipid Research Atherosclerosis Unit, Departments of Pediatrics and Medicine, the Johns Hopkins University School of Medicine, Baltimore, Maryland. This study was supported in part by the Preventive Cardiology Academic Award to Dr. Pearson (5KO7HL01113) and a National Research Scientific Academy Fellowship award to Dr. Miller (5F32HL07596). Manuscript received June 1, 1989; revised manuscript received and accepted August 23, 1989.

Dr. Pearson's present address: the Research Institute of the Mary Imogene Bassett Hospital, Cooperstown, New York.

Address for reprints: Michael Miller, MD, Division of Cardiology, Carnegie 568, the Johns Hopkins Hospital, Baltimore, Maryland 21205.

The National Cholesterol Education Program treatment guidelines recommend that all adults with plasma total cholesterol levels >240 mg/dl undergo lipoprotein analysis,[1] because high levels of total cholesterol or low density lipoprotein (LDL) cholesterol are associated with an increased risk of coronary artery disease (CAD) and reduction of these levels decreases coronary events.[2] These guidelines also apply for a total cholesterol between 200 and 239 mg/dl if CAD or ≥2 risk factors for CAD are present. Conversely, a total cholesterol <200 mg/dl is "desirable" and no further lipid or lipoprotein analysis is recommended except for repeat total cholesterol measurements every 5 years.

High density lipoprotein (HDL) cholesterol has received less attention than LDL cholesterol, despite being a strong and independent predictor of CAD.[3] Whether very low density lipoprotein (VLDL) cholesterol, or its predominant lipid, triglyceride, independently predicts CAD has been controversial.[4]

Because the overwhelming majority of lipid or lipoprotein abnormalities (dyslipidemias) coincide with a total cholesterol >200 mg/dl, it is not surprising that data are lacking in CAD subjects with total cholesterol ≤200 mg/dl. We examine this issue.

METHODS

Patient selection: One thousand men and women aged from 26 to 77 years underwent diagnostic coronary arteriography at the Johns Hopkins Hospital between 1975 and 1978. The study population comprised 2 groups: the first consisted of 260 nonconsecutive patients who had arteriograms from April 1975 to March 1977 as part of a pilot study to examine risk factors for CAD. The second group consisted of 740 consecutive patients studied from March 1977 to April 1978. The groups differed in 2 ways. Although selection criteria were the same for groups 1 and 2, only a fraction of eligible patients were included in group 1, whereas all patients were enrolled in group 2. To test for selection bias, groups 1 and 2 were compared with regard to age, sex, race, number of diseased coronary vessels and cardiac history. The significance of differences was tested using the chi-square test. Group 1 had significantly

TABLE I Mean Levels of Plasma Lipids and Lipoproteins With or Without CAD and Total Cholesterol ≤200 mg/dl by Sex

	Men				Women			
	CAD		No CAD		CAD		No CAD	
	No.	Mean ± SD	No.	Mean ± SD	No.	Mean ± SD	No.	Mean ± SD
Age (yrs)	139	56 ± 9†	55	49 ± 11	37	56 ± 10	57	52 ± 9
TC (mg/dl)	139	175 ± 20*	55	167 ± 25	37	176 ± 23	57	169 ± 26
TG (mg/dl)	139	123 ± 62*	55	97 ± 73	37	126 ± 61†	57	85 ± 37
HDL (mg/dl)	138	34 ± 9*	55	40 ± 15	37	39 ± 10*	56	45 ± 12
LDL (mg/dl)	126	119 ± 22*	53	110 ± 21	35	113 ± 25	51	112 ± 26
VLDL (mg/dl)	120	23 ± 14*	50	18 ± 15	34	22 ± 13†	49	12 ± 6
TC:HDL	138	6 ± 2†	55	5 ± 2	37	5 ± 1*	56	4 ± 1
LDL:HDL	126	4 ± 2*	53	3 ± 1	35	3 ± 1	51	3 ± 1

* $p < 0.05$; † $p < 0.001$.
CAD = coronary artery disease; HDL = high density lipoprotein; LDL = low density lipoprotein; SD = standard deviation; TC = total cholesterol; TG = triglycerides; VLDL = very low density lipoprotein.

more patients ($p < 0.05$) who were <50 years old (43 vs 35%) and black (11 vs 7%). However, groups 1 and 2 did not differ by sex (67% were men), presence of angina or history of myocardial infarction. Most importantly, the 2 groups were very similar with respect to the presence or extent of CAD. We therefore combined groups 1 and 2 in the analysis.

Coronary arteriography: After cardiac catheterization, each angiogram was reviewed by 3 cardiologists who were blinded to patient identity and the initial angiographic report. There was an 88 to 95% agreement between this panel and the catheterization report. The location and severity of disease (as percent of luminal narrowing) was recorded in 15 segments of the 3 main coronary arteries and the left main coronary artery as previously described.[5] Patients with a luminal diameter reduction of ≥50% of any coronary artery segment were classified as having angiographically demonstrated CAD.

Lipid and lipoprotein analysis: Plasma lipid and lipoprotein levels were determined at the Johns Hopkins Lipid Research Clinic, a laboratory standardized by the Centers for Disease Control. On the morning of arteriography after an overnight fast, 15 ml of venous blood was collected in a single vacutainer tube containing disodium ethylenediaminetetraacetic acid. Plasma cholesterol and triglyceride levels were measured with a Technicon Auto Analyzer II (Technicon Instrument Corp.), using modified Lieberman-Burchard and fluorometric techniques, respectively. HDL cholesterol was determined after precipitation of the apo-B containing lipoproteins in plasma with heparin-manganese. Plasma (5 ml at its own density) was subjected to ultracentrifugation at 105,000 g for 18 hours; VLDL cholesterol and LDL cholesterol were determined using methods of the Lipid Research Clinics Program.[6] Ultracentrifugation was performed in 87% of men and 85% of women. In the remaining cases, LDL cholesterol was estimated from the Friedewald formula[7] (neither chylomicronemia nor triglycerides >400 mg/dl was present). Agarose gel electrophoresis was used to detect the presence of floating β lipoproteins in the d <1.006 ultracentrifugal supernatant indicative of type III hyperlipoproteinemia (dysbetalipoproteinemia), or of sinking pre-β lipoproteins [LP(a)] in the d >1.006 ultracentrifugal infranate. The average threshold for detectability of Lp(a) is 21 mg/dl.[8] Of the 1,000 patients, approximately 6% did not have lipid analyses performed, primarily because heparin had been administered before sampling.

Lipoprotein levels were categorized for univariate analyses based on current National Cholesterol Education Program guidelines. The cutoff levels were total cholesterol of 200 mg/dl, LDL cholesterol of 130 mg/dl and HDL cholesterol of 35 mg/dl. An HDL cholesterol of 45 mg/dl was also tested in woman because this represents the bottom quartile and more closely approximates the 35 mg/dl cutoff level in men.[9] Because criteria for "desirable" triglyceride levels are not well established, we arbitrarily chose 150 mg/dl, which approximates the 50th to 75th percentile in adult men and the 75th to 90th percentile in women.[9] Lipoprotein phenotypes based on the Fredrickson-Levy classification[10] were also determined.

Risk factor assessment: Risk factor assessment was determined by self-administered questionnaires and medical record review. They included: age (>50 years in men and >60 years in women), a family history of at least 1 first-degree relative with known coronary disease, current smoking history (≥1 cigarette smoked/day), physical activity (participant in a regular exercise program),[11] body mass index (weight [in kg] divided by height [in m^2] on admission, with obesity defined as >27),[12] hypertension (>140/90 mm Hg at admission or while receiving antihypertensive medication), alcohol consumption (>1 drink/day), diabetes mellitus (by history, use of hypoglycemic agents or fasting blood sugar >115 mg/dl on admission). The medication status of all subjects was also recorded.

Statistical analysis: Patients were grouped into those with and without CAD. The differences in continuous risk factor variables between these groups were evaluated using the *t* test. The differences in categorical variables were measured using chi-square tests. The designated level of significance was 0.05. Multiple logistic regression analysis evaluated the effects of risk factors on the occurrence of CAD. The significance of the coefficients was tested using the Wald statistic. All

analyses were stratified by sex and total cholesterol level (≤200 and >200 mg/dl) using the Statistical Analysis System computer program.

RESULTS

One thousand patients undergoing diagnostic coronary angiography were subdivided into 2 groups: desirable total cholesterol levels (≤200 mg/dl) and borderline or high levels (>200 mg/dl). There were 935 patients who had lipid analyses performed; 351 had total cholesterol ≤200 mg/dl. Of 244 men and 107 women with total cholesterol ≤200 mg/dl, CAD was present in 76% of men and 44% of women ($p < 0.01$); the distribution of CAD by gender was similar to the total cholesterol >200 mg/dl group (88% of men, 51% of women). The prevalence of CAD in whites and blacks with total cholesterol ≤200 mg/dl (67 vs 59%) and >200 mg/dl (78 vs 73%) was not significantly different.

The subsequent series of data analyses focused exclusively on the group with total cholesterol ≤200 mg/dl. Patients (50 men, 13 women) with a recent myocardial infarction (<2 months) were excluded, because lipoprotein levels are altered during this period.[13] Table I lists the significant differences in mean ages, lipid and lipoprotein levels between CAD and non-CAD men. In women, only mean triglycerides, VLDL cholesterol and HDL cholesterol levels were statistically different. Mean ratios of total cholesterol to HDL cholesterol were also significantly higher in men and women with CAD.

Table II lists results of univariate analysis for the risk factors studied. Older age, systemic hypertension (in men) and diabetes mellitus (in both sexes) were significantly prevalent in CAD subjects with desirable total cholesterol levels. Figure 1 shows the significant prevalence of low HDL cholesterol in men and women with CAD. Approximately 67% of men with CAD and 33% of women with CAD had HDL cholesterol ≤35 mg/dl, and 80% of women with CAD had HDL cholesterol ≤45 mg/dl. No significant differences in prevalence of high LDL cholesterol or triglycerides were noted.

TABLE II Prevalence of Selected Risk Factors in Men and Women With or Without CAD and Total Cholesterol ≤200 mg/dl

	Men				Women			
	CAD		No CAD		CAD		No CAD	
	No.	%	No.	%	No.	%	No.	%
Family history (+)	122	66	46	50	33	79	48	73
Cigarette smoker	133	82	51	71	35	57	54	48
Hypertension	138	44*	55	24	36	44	57	26
Age	139	71†	55	44	37	35	57	21
Exercise	121	28	46	24	33	21	49	31
Alcohol	122	24	46	24	33	6	48	15
Body mass index >27	122	25	49	31	29	24	42	21
Diabetes mellitus	137	14*	54	2	37	27†	57	4
Lp(a) positive	117	3	48	4	30	17	47	4

* $p < 0.05$; † $p < 0.001$.
CAD = coronary artery disease.

There were 24 patients meeting the criteria of the Fredrickson-Levy classification; 20 men and 4 women had type IV lipoprotein patterns. Chylomicronemia was not detected in the plasma samples analyzed.

Pharmaceuticals that may impact adversely on plasma lipids and lipoproteins include β blockers and thia-

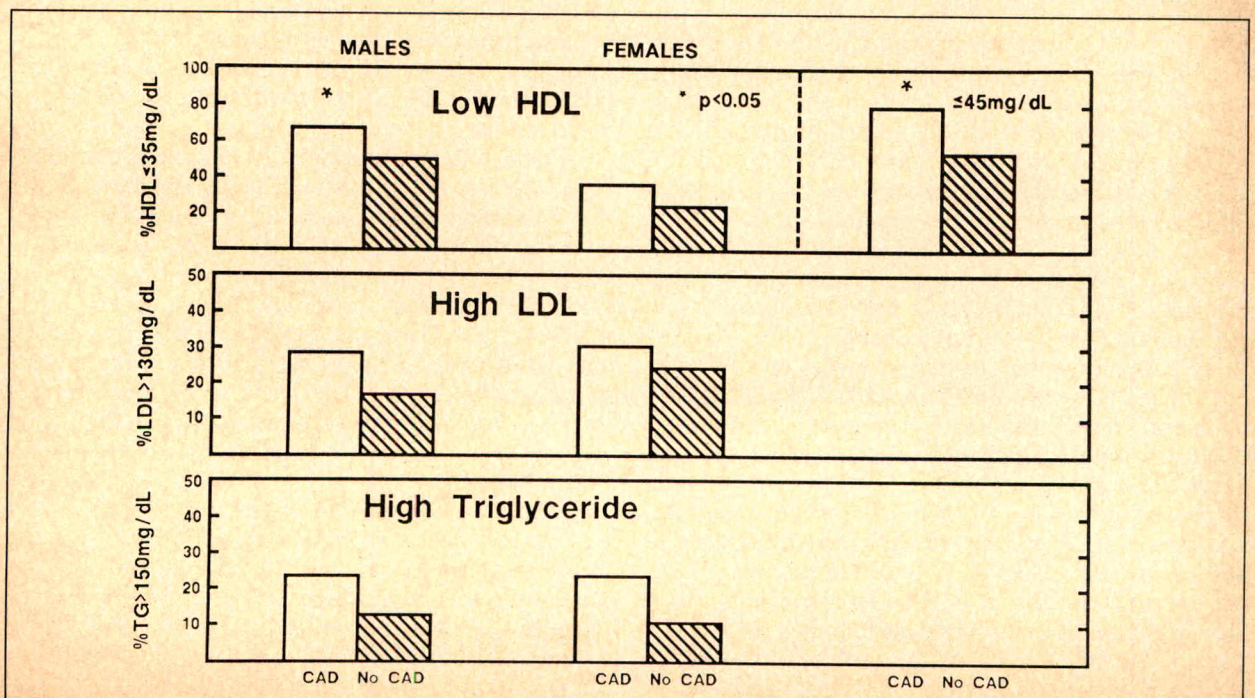


FIGURE 1. Prevalence of lipid and lipoprotein abnormalities with or without coronary artery disease (CAD) and total cholesterol ≤200 mg/dl. HDL = high density lipoprotein; LDL = low density lipoprotein; TG = triglyceride.

TABLE III Mean Lipid and Lipoprotein Levels in CAD Subjects With or Without β Blockers or Thiazide Diuretics and Total Cholesterol ≤200 mg/dl

	Men				Women			
	With		Without		With		Without	
	No.	Mean ± SD	No.	Mean ± SD	No.	Mean ± SD	No.	Mean ± SD
β Blockers								
HDL	67	34 ± 9	70	33 ± 8	17	37 ± 10	20	41 ± 10
LDL	59	119 ± 21	66	118 ± 23	17	112 ± 21	18	113 ± 28
TG	67	133 ± 62	71	114 ± 62	17	149 ± 77*	20	105 ± 32
Thiazide Diuretics								
HDL	20	31 ± 5	89	34 ± 8	6	44 ± 7	15	39 ± 10
LDL	19	129 ± 18*	80	118 ± 22	4	116 ± 15	15	119 ± 18
TG	21	122 ± 61	89	133 ± 65	6	104 ± 26	15	133 ± 63

* $p < 0.05$.
Abbreviations as in Table I.

TABLE IV Multiple Logistic Regression Analysis of CAD with Selected Risk Factors and Total Cholesterol ≤200 mg/dl

	Men (n = 150)			Women (n = 64)		
Variable	Coefficient	SE	p Value	Coefficient	SE	p Value
Age	0.0710	0.0221	0.001	0.0042	0.0340	NS
VLDL	0.0223	0.0160	NS	0.1736	0.0551	0.002
HDL	−0.0518	0.0218	0.018	0.0053	0.0309	NS
Hypertension	1.3412	0.4979	0.007	0.3032	0.6805	NS
Body mass index	−0.0810	0.0532	NS	−0.0656	0.0703	NS

NS = not significant; SE = standard error. Other abbreviations as in Table I.

zide diuretics.[14] Although 49% of men with CAD (137) and 46% of women with CAD (37) were receiving β blockers, the prevalence of low HDL cholesterol (≤35) was not significantly different between the β-blocker and non-β-blocker groups (66 vs 71% in men; 41 vs 25% in women). Mean lipid and lipoprotein levels in CAD subjects with or without β-blocker or thiazide use is listed in Table III. Significantly higher mean LDL cholesterol in men, and triglycerides in women, accompanied thiazide and β-blocker use, respectively. Mean HDL cholesterol levels were not significantly altered with use of either drug. Furthermore, mean HDL cholesterol in CAD subjects receiving β blockers was not statistically different than in the non-CAD control subjects (34 vs 36 mg/dl in men; 41 vs 43 mg/dl in women). In addition to these drugs, 8 women were using estrogen supplements or oral contraceptives and 5 men were receiving clofibrate for hypertriglyceridemia.

A multiple logistic regression model of CAD was constructed using age, HDL cholesterol, VLDL cholesterol, body mass index and hypertension (Table IV) as the independent variables. Diabetes mellitus was not added to the model due to the small number of diabetic subjects without CAD (1 man and 2 women). In men, age, plasma HDL cholesterol and hypertension were independently correlated with CAD. In women, VLDL cholesterol was the sole variable independently associated with CAD, after adjustment for other risk factors. The addition of β blockers to the model did not alter the significant independent effect of HDL cholesterol in men ($p = 0.02$) or VLDL cholesterol in women ($p = 0.002$).

DISCUSSION

The National Cholesterol Education Program recently established guidelines for the detection and management of hyperlipidemia and is predicated on the results of a screening of total cholesterol. If a total cholesterol level is <200 mg/dl, reassurance is provided and cholesterol measurements need not be repeated for up to 5 years thereafter. There is no allowance for lipid or lipoprotein analysis. Hence, atherogenic dyslipidemias present despite desirable cholesterol levels will not be detected under the current system.

Although the incidence of CAD increases considerably as cholesterol levels increase >200 mg/dl,[1] evidence that a desirable total cholesterol does not afford immunity from CAD is exemplified in the Framingham Study, where >15% of middle-aged adults developing CAD over a 12-year period had total cholesterol levels <200 mg/dl.[15] The high prevalence of desirable cholesterol levels (34%) among CAD patients in the present study is noteworthy; despite these levels, HDL cholesterol was independently associated with CAD in men, even after adjustment for other confounding variables (i.e., β blockers).

That low levels of HDL cholesterol predict CAD is well documented in hyperlipidemic patients.[16] Results from long-term prospective studies[17,18] now support similar conclusions even when cholesterol levels are not elevated. Our data provide further evidence that a total cholesterol in the desirable range may underestimate the importance of HDL cholesterol.

The role of VLDL cholesterol (or triglycerides) as an independent predictor of coronary disease remains

unresolved, although it has been demonstrated in women and men aged >50 years.[19] Recently, triglycerides were a significant predictor of coronary death when total cholesterol levels were <220 mg/dl; several potential mechanisms have been postulated.[20] In the present study, VLDL cholesterol was the only independent variable associated with CAD in women. Mean triglyceride levels were also significantly higher in both men and women with CAD (Table II) than in non-CAD patients. Normal or mildly elevated plasma triglycerides (150 to 250 mg/dl) often occur in hyperapobetalipoproteinemia (hyperapoB), a lipid disorder marked by increased levels of the major apolipoprotein of LDL, apo B, and an increased risk of CAD in the presence of a normal or near-normal LDL cholesterol.[21] Apolipoproteins were not measured in this study and consequently, the prevalence of this disorder could not be ascertained.

Identification of low HDL cholesterol or high triglyceride levels in CAD patients is warranted because they may be potentially modifiable through smoking cessation,[22] aerobic exercise,[23] weight reduction, fat-modified diets and drugs. Dietary restriction decreases triglyceride and increases HDL cholesterol levels in obese subjects.[1] Unfortunately, there are no unique HDL cholesterol-raising diets; the objective therefore, is to improve the total or LDL cholesterol to HDL cholesterol ratio by substituting poly- or monounsaturated for saturated fats.[24]

Pharmaceuticals may be tried if traditional measures fail. Elevations in HDL cholesterol up to 37% and reductions in triglycerides by 40% have been achieved with these agents.[25,26] More importantly, dietary or pharmacologic manipulation, which significantly increase HDL cholesterol while decreasing LDL cholesterol or triglycerides, may halt progression of existing atherosclerotic lesions,[27,28] even in the setting of a "desirable" total cholesterol.[26] This is of considerable significance for men with CAD, in whom, even in the presence of desirable cholesterol levels, the incidence of further coronary events (myocardial infarction or sudden death) is nearly 9-fold greater than for men without CAD.[29]

It has recently been demonstrated that increasing HDL cholesterol independently reduces future CAD events in hyperlipidemic subjects.[30] Whether the same is applicable in subjects with isolated low HDL cholesterol levels but desirable total cholesterol levels is an area that merits further investigation. Presently, we believe that secondary preventive measures should be maximized in all CAD subjects, and therefore complete lipid and lipoprotein analysis should be made a routine part of this approach.

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Blood Cholesterol Screening in Several Environments Using a Portable, Dry-Chemistry Analyzer and Fingerstick Blood Samples

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A multicenter study of blood cholesterol screening was performed in several typical environments, such as community sites (shopping malls and a supermarket), health care sites, work sites, a blood bank and a school. Cholesterol was measured with a portable, dry-chemistry analyzer using capillary blood obtained by fingerstick. Data are reported from a total of 13,824 participants, spanning the entire age spectrum. Overall, 25% of screened subjects had blood cholesterol levels above the age-specific cutpoints used in the current study. Although in the aggregate this screening experience very closely approximates the expected level of referrals, the proportion of referred screened subjects differed significantly among the 5 types of screening environments and by gender. Follow-up telephone interviews indicated that 53% of referrals had initiated a physician contact. More than 75% of those who had seen a physician reported that the diagnosis of hypercholesterolemia had been confirmed, and almost 72% had been prescribed a diet. A large proportion of referred screened subjects reported having modified their diet, particularly when recommended to do so by a physician. This study has yielded encouraging evidence that physicians gave referred screened subjects appropriate initial advice for managing hypercholesterolemia. The new technology for blood cholesterol measurement evaluated in the current study has proven to be a feasible and reliable means for measuring blood cholesterol in typical screening settings.

(Am J Cardiol 1990;65:6–13)

Widespread enthusiasm for conducting public screening to measure blood cholesterol has become increasingly evident, reflecting the growing public awareness that high blood cholesterol is a major and controllable risk factor for coronary heart disease and that it is important to know one's cholesterol level.[1] We used new technology to measure cholesterol from capillary blood obtained by fingerstick. This technology offers the attractive features of instrument portability, minimal discomfort, availability of test results within minutes and low single-test cost.

Screenings were performed at health-care sites and several public screening environments. Follow-up telephone interviews were done to evaluate screened subjects' compliance with referral recommendations and to ascertain physician management of referred screened subjects. Four major questions were addressed: (1) What proportion of screened subjects have blood cholesterol above referral levels? (2) Do referred screened subjects visit a physician? (3) When screened subjects visit a physician, is the diagnosis of high cholesterol confirmed and are dietary changes prescribed by the physician? (4) Is physician prescription of dietary modification necessary for its adoption by screened subjects with blood cholesterol levels above referral cutpoints?

METHODS

Participating centers, environments screened and recruitment: Studies by the 11 United States Lipid Research Clinics involved screenings in blood banks (conducted by 1 center), and school (1 center), community (4 centers), health care (4 centers) and work sites (3 centers), performed according to collaborative protocols. The recruitment strategy involved a limited effort at each center to disseminate information concerning the site locations and dates of the screenings. Participation by screened subjects was voluntary.

Cholesterol measurement: Cholesterol measurements were performed using the Reflotron®, a portable, dry-chemistry analyzer, manufactured by Boehringer-Mannheim. A 30-μl sample of whole blood, collected via fingerstick into a heparinized capillary tube, is applied to the obverse side of the reagent tab. With this procedure, erythrocytes are separated from plasma on a glass-fiber layer at the surface of the tab. The plasma flows by capillary action into a sequence of layers containing reagents for an enzymatic method, in which cholesteryl esters are hydrolyzed by cholesteryl esterase, followed by oxidation of the unesterified cholesterol catalyzed by cholesterol oxidase. One of the reaction prod-

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*See Appendix.

TABLE I Number of Screened Subjects in Successive Phases of Study

Environment	Phase: No. Screened	Referrals: No.	Referrals: Percent of Category Screened	Follow-Up: No.	Follow-Up: Percent of Category Referred	Follow-Up: Percent of Total Follow-Ups
Blood bank	1,460	246	16.8	55	22.4	4.9
Community	8,281	2,306	27.8	542	23.5	48.7
Health care	2,029	668	32.9	304	45.5	27.3
School	586	101	17.2	31	30.7	2.8
Work	1,468	210	14.3	181	86.2	16.3
Total	13,824	3,531	25.5	1,113	31.5	100.0

TABLE II Mean Reflotron® Cholesterol* by Age Group and Screening Environment

Age (yrs)	Screening Environment: Blood Bank	Community	Health Care	School	Work	Total
<20				147		147
No.				586		586
20–29	170	179	176		164	173
No.	362	419	203		234	1,218
30–39	185	189	190		180	186
No.	509	925	217		479	2,130
≥40	205	219	225		202	218
No.	589	6,937	1,609		755	9,890
Total	190	214	216	147	189	206
No.	1,460	8,281	2,029	586	1,468	13,824

* Cholesterol values are in mg/dl.

ucts, hydrogen peroxide, then oxidizes a dye to produce a colored product that is measured with a reflectance photometer.

A magnetic strip affixed to the reverse side of the reagent tab contains test-specific information, including parameters of the analysis procedure and calibration data to convert photometer readings into cholesterol values. After the blood sample has been applied, the reagent tab is inserted immediately into the analyzer unit. The cholesterol reading is displayed on a digital readout, after an elapsed analysis time of about 3 minutes.

Quality control of cholesterol measurements: A check tab provided by the Reflotron manufacturer was used at least once at the beginning of each day's screening to verify that the reflectance photometer unit was operating within prescribed limits. In addition, aliquots from each of 2 quality control samples (Precinorm U®, mean cholesterol 196 mg/dl; and Precipath U®, mean cholesterol 239 mg/dl), provided by Boehringer-Mannheim, were analyzed after each vial (26 tabs) of reagent tabs to monitor the performance of the entire system. Cholesterol readings obtained with these controls had to remain within 2 standard deviations of the mean (the range of acceptable values specified in the instructions accompanying each control sample vial) for analysis to continue.

Referral guidelines: In our study, conducted before release of the new National Cholesterol Education Program adult treatment guidelines,[2] the blood cholesterol levels that prompted a referral of screened subjects aged ≥20 years to a physician for follow-up evaluation were defined using the age-specific cutpoints recommended by the National Institutes of Health Consensus Development Conference on Lowering Blood Cholesterol.[3] Blood cholesterol values ≥90 percentile of the Lipid Research Clinics Prevalence Study[4] were designated as the high-risk category, whereas those between the 75th and 90th percentiles were designated as the moderate-risk group. Participants <20 years of age were referred if the blood cholesterol was ≥180 mg/dl. These referrals were not further subdivided into high- and moderate-risk categories.

At the screening site, each screened subject was provided a form that recorded the cholesterol result and was also advised to seek follow-up evaluation by a physician if the screening value was within the referral range. Information printed on this form listed the cutpoints defining moderate- and high-risk cholesterol levels and recommended that screened subjects with elevated cholesterol levels consult their physician for follow-up evaluation. A copy of this form was mailed to the designated physician when requested by the screened subject. Each screened subject was also given an informative brochure concerning blood cholesterol and other coronary artery disease risk factors that also included dietary advice for lowering blood cholesterol. In addition, dieticians or other staff were usually available at the screenings to answer questions.

Follow-up survey of referred screened subjects: Table I lists the number of participants from each screening environment who were included in the follow-up phase of this study. Within several weeks (median 2 months) after the screening, a telephone interview was conducted with a total of 1,113 (31%) of the referred

screenees. Participants whose blood cholesterol levels were in the referral range were selected at random for follow-up by telephone interview. If efforts to contact a specific individual were unsuccessful after 3 attempts, the next randomly selected referral was contacted until the designated number (generally approximately 100/center) of follow-up interviews were completed. None of those contacted refused to provide the requested information.

RESULTS

Mean cholesterol values are listed in Table II by age group and screening environment. A total of 13,824 participants were screened, including 13,238 who were ≥20 years of age, and 586 school-site participants who were <20 years of age. Health care and community sites yielded older (79 and 84%, respectively, aged ≥40 years) and predominantly female (>60%) participants, when compared with work sites (51% were 40 years or

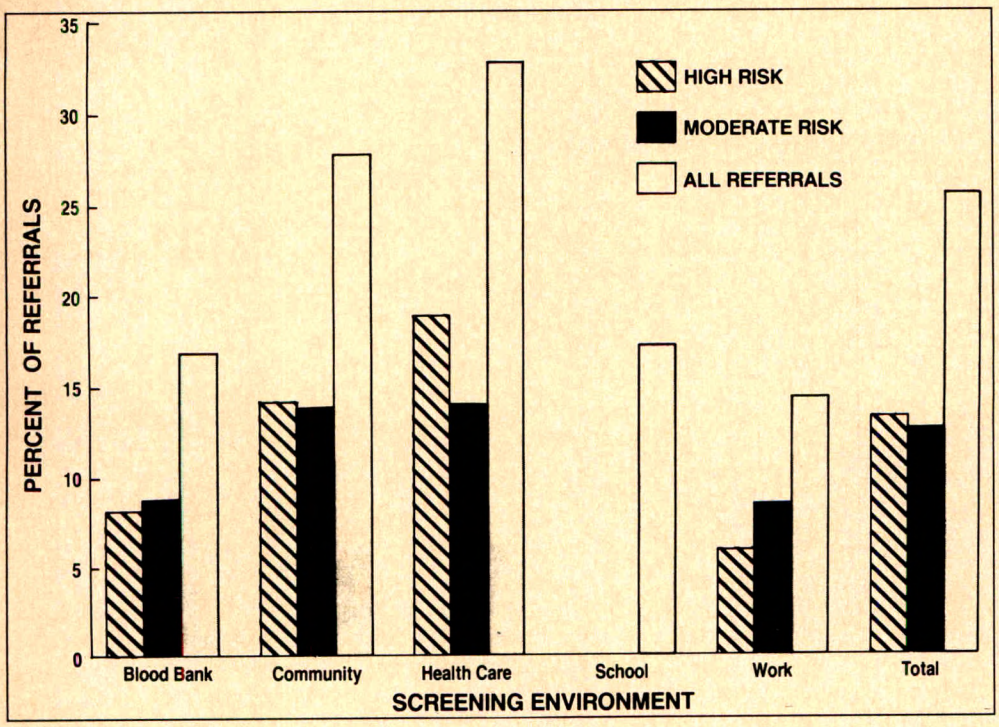


FIGURE 1. Proportion of referred screened subjects, categorized by screening environment. School site screened subjects are included only in the "all referrals" values, because a single referral cutpoint (blood cholesterol ≥180 mg/dl) was used for the school site (<20 years) group.

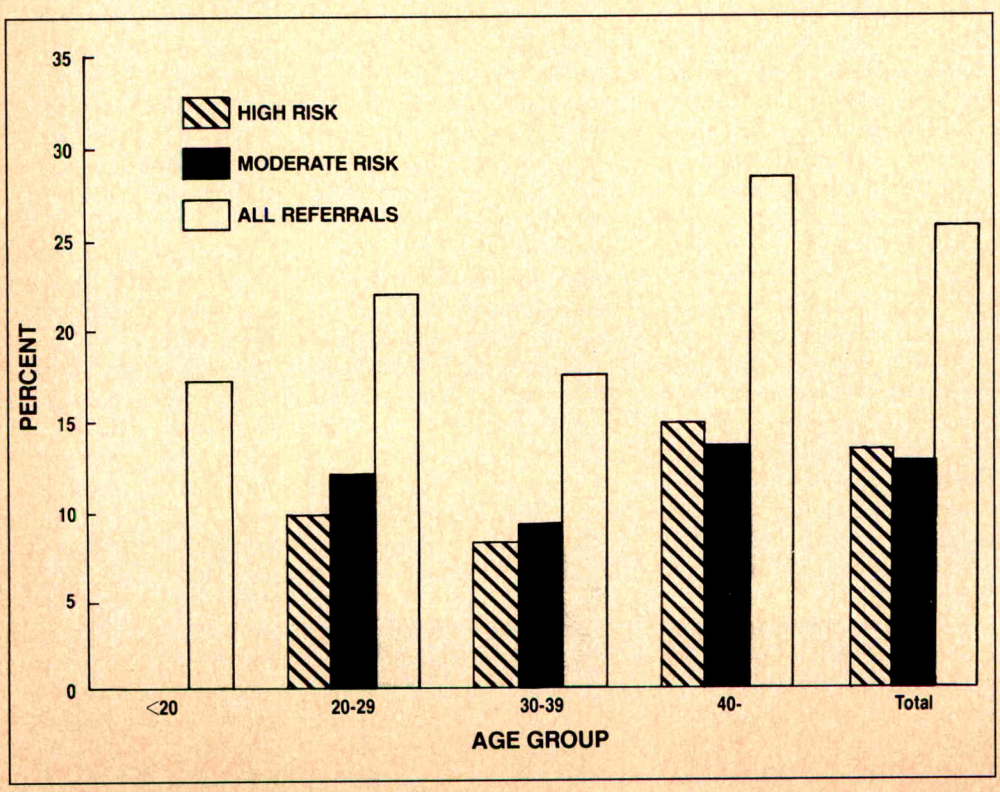


FIGURE 2. Proportion of referred screened subjects, categorized by age. School site screened subjects are included only in the "all referrals" values, because a single referral cutpoint (blood cholesterol ≥180 mg/dl) was used for the school site (<20 years) group.

older and 52% were men) or blood banks (40% were 40 years or older, and 55% were men).

Figure 1 shows the proportion of screening values that fell within the referral range, categorized according to screening environment. The overall proportion of referrals was 25%, including equal proportions of those in the high- and moderate-risk categories. The proportion of referrals differed ($p < 0.01$) among the screening environments, with the lowest levels in screened subjects from blood banks and work sites. The proportion of referrals also differed among age groups, even though the cutpoints were age-specific (Figure 2). Screened subjects aged ≥40 years had the highest proportion of blood cholesterol levels above the referral cutpoints. Fewer men (21%) than women (29%) were referred (Figure 3). The proportion of men referred was also

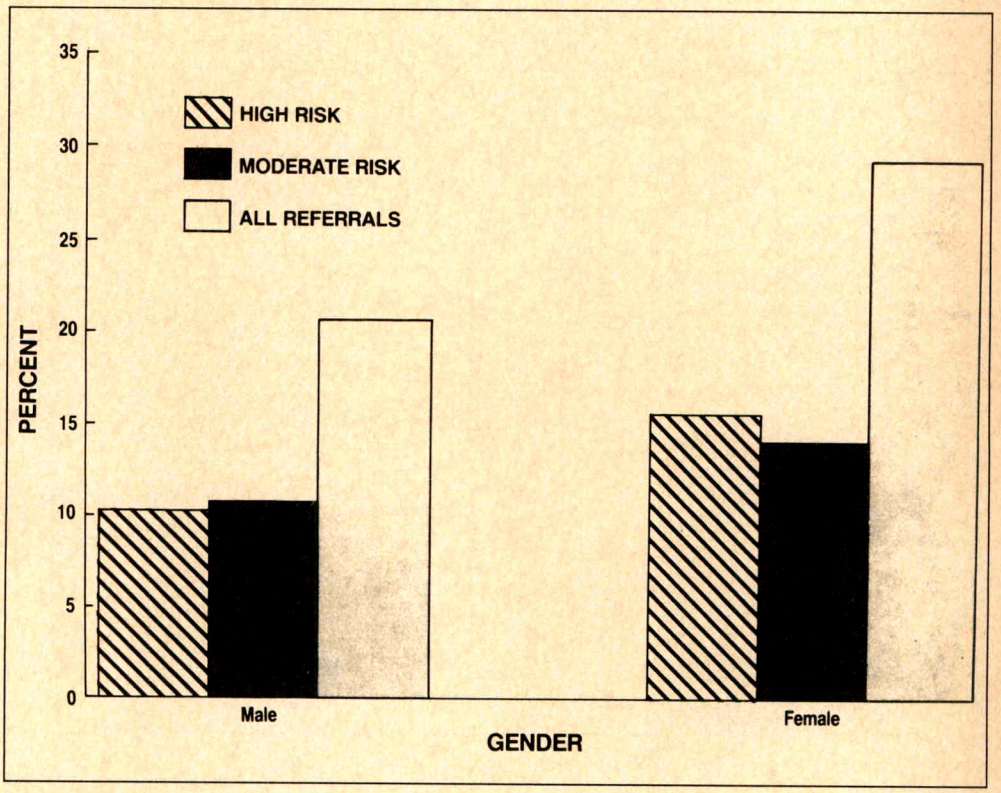


FIGURE 3. Proportion of referred screened subjects, categorized by gender. School site screened subjects are included only in the "all referrals" values, because a single referral cutpoint (blood cholesterol ≥180 mg/dl) was used for the school site (<20 years) group.

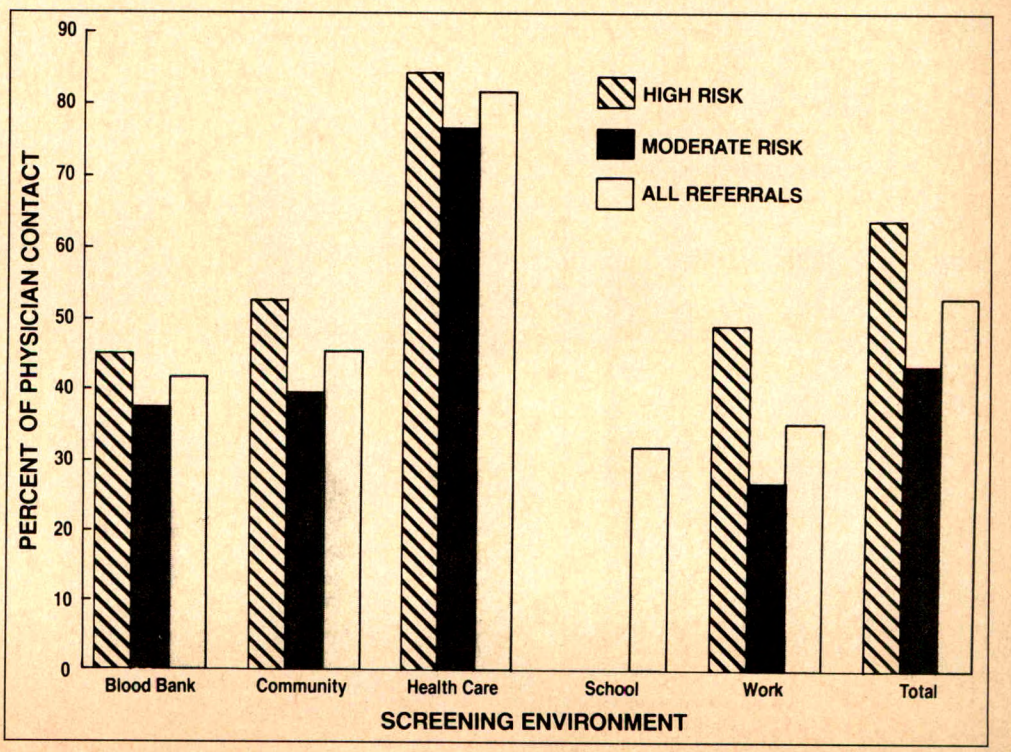


FIGURE 4. Physician contact (visit completed or appointment made) by referred screened subjects, categorized by screening environment. School site screened subjects are included only in the "all referrals" values, because a single referral cutpoint (blood cholesterol ≥180 mg/dl) was used for the school site (<20 years) group.

lower than women in the high-risk (10 vs 16% of those aged ≥20 years) and the moderate-risk groups (11 vs 14%).

Figure 4 shows the response given when referrals from each screening environment were subsequently asked whether they had contacted a physician. More than 53% of those interviewed indicated that they had either seen a physician (43%) or had made an appointment (10%). When the high-risk referrals are compared with those at moderate risk, physician contact (visit completed or appointment made) was reported in a larger proportion of the high- (64%) than moderate-risk (44%) group overall. The highest level of physician contact (82%) was reported by referrals from screenings conducted at health care sites, such as a YMCA cardiac unit, a community health center, a lipid research clinic and a family practice center. The high referral compliance among screened subjects who presented themselves to obtain a cholesterol measurement at 1 of these health care sites was not due to any physician contact that may

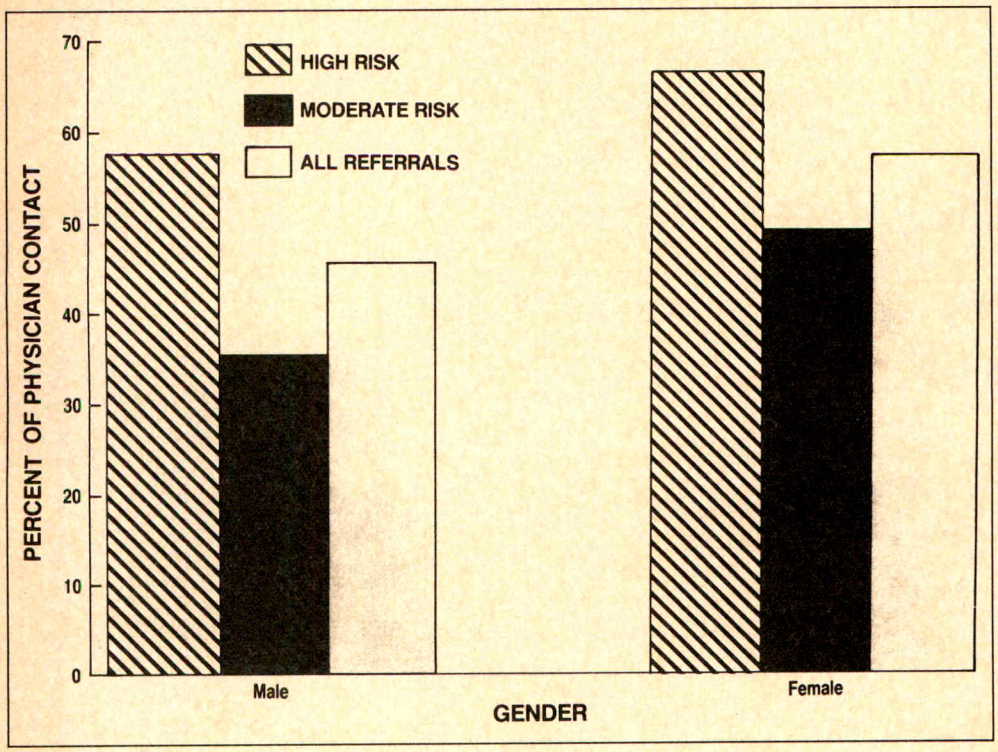


FIGURE 5. Physician contact (visit completed or appointment made) by referred screened subjects, categorized by gender. School site screened subjects are included only in the "all referrals" values, because a single referral cutpoint (blood cholesterol ≥180 mg/dl) was used for the school site (<20 years) group.

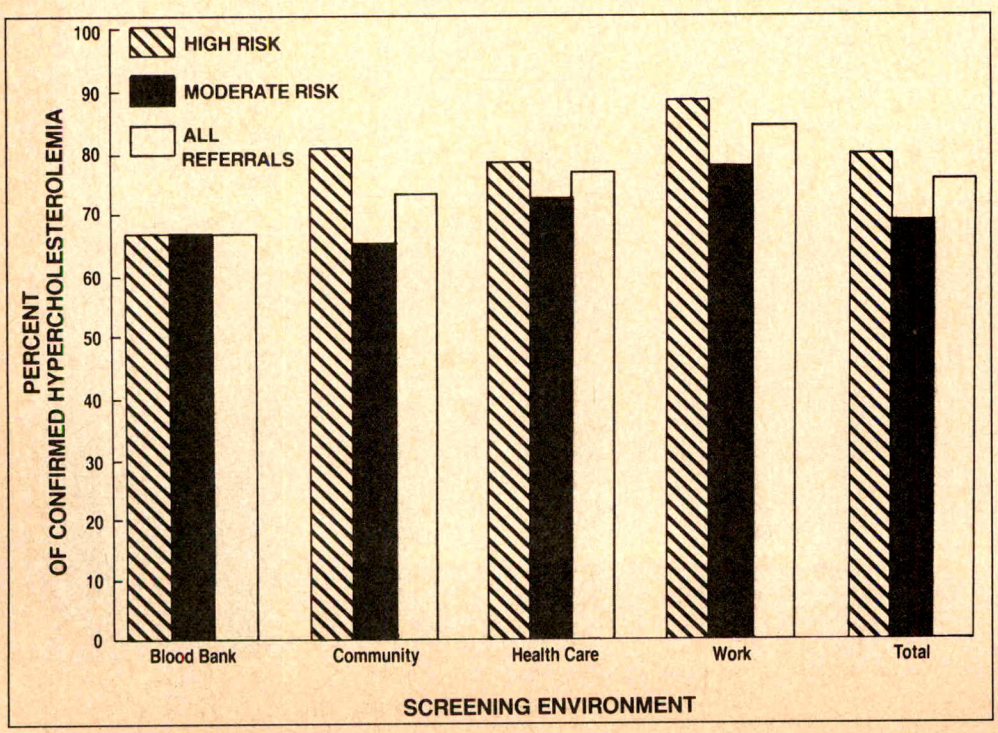


FIGURE 6. Confirmation of hypercholesterolemia by physician, categorized by screening environment. The school site group is not included in these results, because only 8 of the 27 interviewed from the school site screened subjects had completed a physician visit.

have occurred at the time participants were screened, because only those physician contacts that occurred subsequent to the screening visit were included in these tabulations. Figure 5 shows that more women referrals (57%) than men (46%) made physician contact. In each gender, physician contact was more likely in the high- than in the moderate-risk group.

Almost 76% of all referred screened subjects who had seen a physician reported that the diagnosis of hypercholesterolemia was confirmed (Figure 6). This response was slightly more likely in the high-risk referrals (80%) than in those at moderate risk (69%), with little variation among screening sites. Diet modification had been recommended to 72% (Figure 7) of those who had

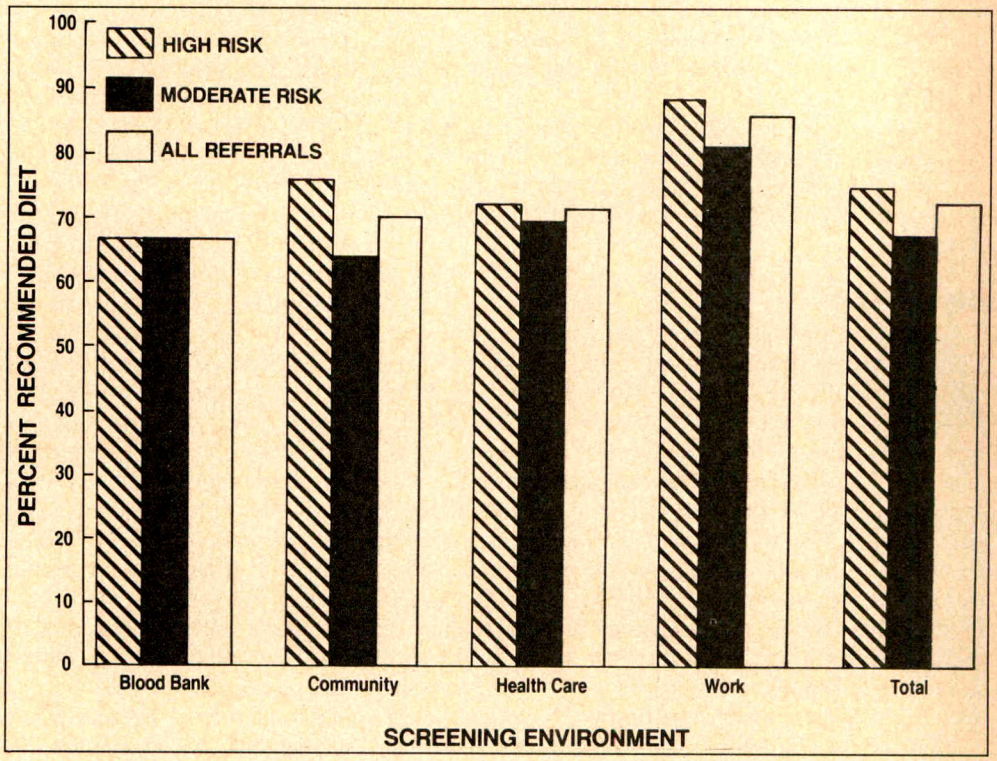


FIGURE 7. Diet recommendation by physician, categorized by screening environment. The school site group is not included in these results, because only 8 of the 27 interviewed from the school site screened subjects had completed a physician visit.

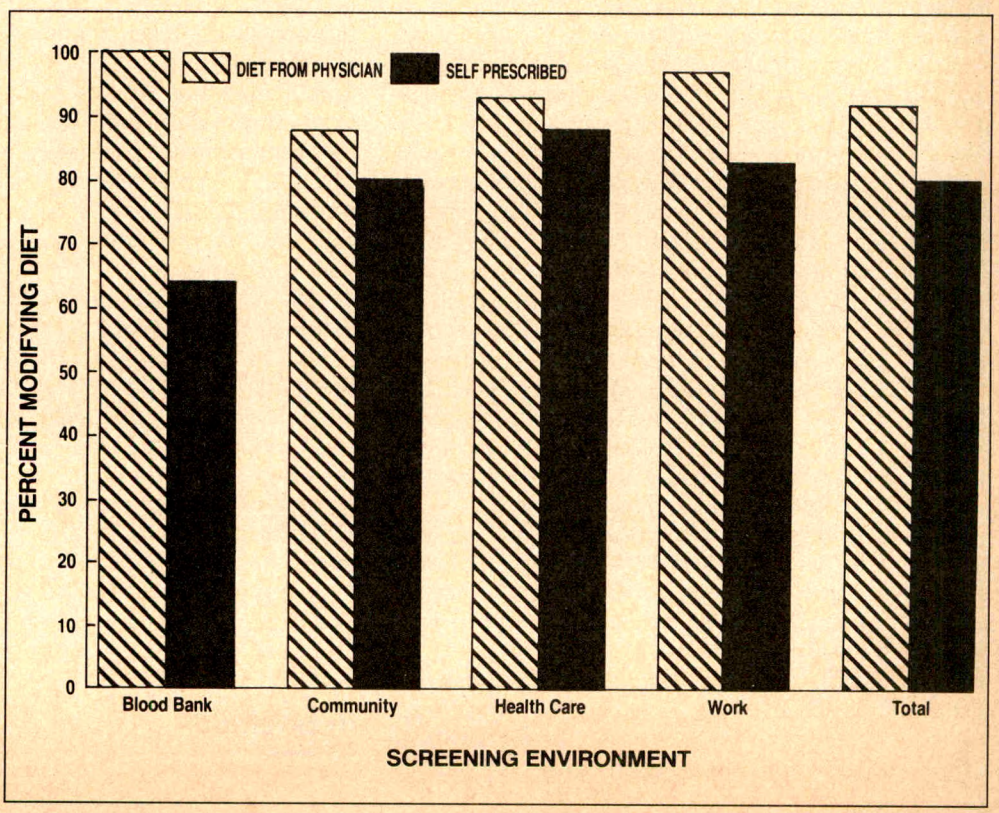


FIGURE 8. Diet modification by referred screened subjects, categorized by screening environment. The school site group is not included in these results, because only 8 of the 27 interviewed from the school site screened subjects had completed a physician visit.

consulted a physician (75% of high-risk referrals vs 68% of those at moderate risk, with the proportion tending to be slightly higher in work site screened subjects than in others). These data were further analyzed to evaluate the relation between the diagnosis of hypercholesterolemia and the prescribing of a diet. Diet modification has been recommended to 87% of those with physician-confirmed hypercholesterolemia. Among those whose physician recommended a diet, 93% reported that the diagnosis of hypercholesterolemia had been confirmed. Similar values were observed in high- and moderate-risk referrals.

A large proportion of referred screened subjects reported that they had modified their diet (Figure 8), including 92% of referrals whose physicians had prescribed a diet and 80% of referrals who had not seen a physician.

DISCUSSION

The effectiveness of intervention strategies for controlling hypercholesterolemia in the population is dependent on properly identifying individuals with high blood cholesterol, with the objective of reducing risk for coronary heart disease through lowering cholesterol. The benefit of knowing one's blood cholesterol level, first advocated in 1984 for all American adults by the National Institutes of Health Consensus Panel,[3] has recently been reaffirmed and will serve as the major public education message of the National Cholesterol Education Program. Detection strategies include case finding in the physician's office or screening in other health care sites, as well as public screening in various environments outside the typical medical setting.[2,3]

We present a large-scale blood cholesterol screening initiative conducted in a multicenter collaboration involving several screening environments (11 health care sites and 4 typical public sites). Concurrent studies[5] of the reliability of cholesterol measurements by the analytical instrument used in the present study indicated that cholesterol values were 0.8 to 3.5% lower in Reflotron-mea-sured capillary samples than in simultaneously obtained venipuncture samples analyzed in Lipid Research Clinics laboratories certified by the Centers for Disease Control. The precision (coefficient of variation), based on the difference between measurements of sequential fingerstick samples from participants, was within 4.3%, sensitivity averaged 94% and specificity was 88%. Calculations based on these observed sensitivity and specificity values indicate that the proportion of referrals will approximate 32% (vs the expected prevalence of 25%), whereas only 2% of those below the cutpoint (75th percentile) will be false negatives.

The mean cholesterol values listed in Table II indicate the expected trend upward with age, and are in general agreement with the values obtained from the Lipid Research Clinics Prevalence Study.[4] Data listed in Table II also indicate that the age and gender of screened subjects may vary among screening environments. If the identification of high-risk younger men was one of the major objectives of a public screening project, results from our study indicate that neither health care nor community sites would be as likely as work sites or blood banks to reach men in the 20- to 40-year age bracket.

The proportion of screened subjects in this study who were referred for hypercholesterolemia (25%) agrees very closely to the level (25%) predicted in the National Institutes of Health Consensus Panel recommendations.[3] The high- and moderate-risk groups each comprised more than 12% of the total, compared to the predicted levels of 10% (high-risk) and 15% (moderate-risk). The proportion of women (16%), but not men (10%), in the high-risk group was higher than predicted (10%), whereas the proportion of men (11%), but not women (14%), in the moderate-risk category was lower than predicted (15%).

The follow-up data collected in the present study are encouraging in respect to the initial compliance of referred screened subjects. More than half of the referrals had either visited a physician or scheduled an appointment by the time of the follow-up telephone interview. In addition, the initial action of their physicians was consistent with the National Institutes of Health Consensus Panel recommendations.[3] They confirmed the diagnosis of hypercholesterolemia in almost 76% of those interviewed and recommended a diet in 72%. The association of a physician-confirmed diagnosis of hypercholesterolemia and the prescribing of a diet was very high (≥87%). Although some caution is appropriate in interpreting self-reported follow-up data, it seems noteworthy that a high proportion of referred screened subjects who had not consulted a physician indicated that they had modified their diet. This response, while encouraging insofar as it reflects behavioral modification in a manner that is consistent with the proper management of hypercholesterolemia, is nonetheless of some concern: this action was taken without first consulting a physician to confirm the diagnosis of hypercholesterolemia. This finding and the fact that almost half of referred screened subjects had not contacted a physician indicate the need to emphasize strongly to referred screened subjects that a high cholesterol value at screening must be confirmed to establish the diagnosis of hypercholesterolemia and that they should seek timely follow-up evaluation by a physician.

The National Institutes of Health Consensus Panel[3] indicated a preference for blood cholesterol screening conducted in the physician's office or other health care site, until the results of feasibility studies concerning public screening were available. Findings from this study confirm the feasibility of using a portable, dry-chemistry analyzer and capillary blood obtained by fingerstick to measure blood cholesterol at typical public screening sites, as well as in the health care environment. Two recent reports have also described public screening projects, conducted at a single[6] or at several[7] local sites, for measuring blood cholesterol using a dry-chemistry analyzer and capillary blood samples.

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APPENDIX
Participating Centers and Key Personnel

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Planning Committee: A. Gotto, MD (Chairman), J. Albers, PhD, P. Bachorik, PhD, G. Cooper, MD, W. Insull, MD, B. Rifkind, MD, A. Tyroler, MD, and D. Williams, PhD.

Relation of Silent Myocardial Ischemia After Coronary Artery Bypass Grafting to Angiographic Completeness of Revascularization and Long-Term Prognosis

Harold L. Kennedy, MD, MPH, Sondra M. Seiler, BA, Michael K. Sprague, Sharon M. Homan, PhD, James A. Whitlock, MPH, Morton J. Kern, MD, Michel G. Vandormael, MD, Hendrick B. Barner, MD, John E. Codd, MD, and Vallee L. Willman, MD, with the technical assistance of Debra Lyyski

The prevalence and characteristics of silent myocardial ischemia as detected by 24-hour ambulatory electrocardiography ST-segment depression were prospectively assessed in 94 patients examined early (1 to 3 months) and 184 patients examined late (12 months) after coronary artery bypass grafting (CABG), and followed for a mean of 48 ± 11 (range 4 to 62) months. The relation of ambulatory electrocardiographic silent ischemia to evidence of completeness of revascularization as defined by cardiac angiography performed 1 and 12 months after CABG, and to prognosis by follow-up of adverse clinical events was analyzed. Silent ischemia was detected early in 20% (19 of 94) and late in 27% (50 of 184) of patients, and showed a mean frequency of episodes ranging from 6 to 10 episodes/24 hours with a mean duration ranging from 15 to 23 minutes. The circadian distribution of episodes disclosed a significant peak of ischemic activity during the period of 6 A.M. to noon and a secondary peak between 6 P.M. and midnight ($p < 0.01$ and $p < 0.001$, respectively). Silent ischemia was not found by univariate analysis to be associated with graft or anastomotic site occlusions, low graft flow rates, grafted arteries with significant distal residual stenoses or ungrafted stenotic native coronary arteries. Kaplan-Meier analysis of time to cardiac event showed that silent ischemia was not predictive of an adverse clinical event in the early years after CABG. Cox regression analysis of 30 covariates only disclosed age (relative risk 1.06 [95% confidence interval, 1.01 to 2.94]) as having an effect on time to adverse clinical event. These data show that ambulatory electrocardiographic-detected silent ischemia during the first year after CABG in patients with predominantly good left ventricular function is not associated with an adverse prognosis.

(Am J Cardiol 1990;65:14–22)

Silent myocardial ischemia has been described and characterized in patients with stable angina pectoris,[1,2] rest and nocturnal angina,[3] unstable angina,[4] asymptomatic coronary artery disease,[5] variant angina pectoris[6] and syndrome X.[7] Early studies have also reported silent myocardial ischemia in patients before and after coronary artery bypass grafting (CABG) as detected by exercise testing and ambulatory electrocardiography.[8–11]

After CABG, myocardial ischemia may result from early or late graft occlusion, low graft blood flow, anastomotic site stenosis or occlusion, significant distal stenoses of grafted arteries or progressive coronary artery disease in ungrafted native vessels. These factors interact in a continuum after CABG, may or may not cause symptoms and are related to prognosis.[12,13] Recent reports indicate that silent myocardial ischemia detected by ambulatory electrocardiography 3 to 5 months after CABG is a valid indicator of myocardial ischemia,[8–10] is associated with incomplete myocardial revascularization[10] and is a powerful predictor of cardiac events in the initial 9 months after surgery.[11]

We report the prevalence and characteristics of silent ischemia as detected by 24-hour ambulatory electrocardiographic (ECG) ST-segment depression in 94 patients examined early (1 to 3 months) and 184 patients examined late (12 months) after CABG, and followed for 62 months (mean 48 ± 11 months). In addition, we analyzed the relation of silent ischemia to angiographic evidence of completeness of revascularization, and the occurrence of adverse clinical events.

METHODS

Study population: From April 1983 to July 1985, patients aged 21 to 69 years undergoing CABG were eligible for enrollment to a double-blind, randomized,

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placebo-controlled clinical trial assessing the efficacy of therapy of dipyridamole and aspirin to prevent graft occlusion.[14,15] Informed consent was obtained to permit repeat catheterization and angiography 1 to 3 and 12 months after CABG. All enrolled patients were randomized (blinded) to either dipyridamole and aspirin therapy or placebo. Clinical follow-up was obtained 1 month after CABG, thereafter every 3 months to 1986, and subsequently every 6 months. Ambulatory ECG (24-hour) recordings were obtained in-hospital preoperatively (within 1 week) and 1 month after CABG, and out-of-hospital during daily activity 1 to 3, 12 and 24 months after CABG. After the 12-month repeat cardiac catheterization, all participants were removed from blinded therapy, advised to continue open-label dipyridamole (225 mg/day) and aspirin (325 mg/day) or aspirin alone, and followed prospectively. Referral patterns precluded obtaining an exercise stress test during the initial year after CABG.

Of 359 eligible patients, 328 (91%) enrolled, and repeat catheterizations were obtained 1 to 3 months after CABG (early) in 240 (73%) patients, and at 12 months (late) in 224 (68%) patients. Of 240 early patients ambulatory electrocardiography was obtained in-hospital 1 month after CABG in 180 (75%) patients, and out-of-hospital during daily activity 1 to 3 months after CABG in 103 (43%) patients. Of the 224 late patients ambulatory electrocardiography was obtained out-of-hospital in 195 (87%) patients at 12 months. During the trial, interpretive aspects of ambulatory ECG ischemia showed the importance of daily activity on its occurrence,[2] and the persistence of ECG changes after CABG for 1 to 2 months in some patients was recognized. Therefore, the study population was selected to be those patients with out-of-hospital ambulatory electrocardiography and concurrent cardiac catheterization. These criteria were met by 103 early patients and 195 late patients, including 58 patients who underwent both examinations. Furthermore, 9 early patients and 11 late patients were excluded because of the ECG presence of bundle branch block, intraventricular conduction defects, cardiac pacemaker or technically inadequate recordings. Thus, the study groups consisted of 94 early patients and 184 late patients.

Surgery: Surgery was performed using cold blood potassium cardioplegia, systemic hypothermia from 25 to 28°C, topical hypothermia with ice slush and a single ischemic interval for all distal anastomoses. The total surgeries resulted in 568 distal anastomoses with saphenous vein and 130 distal anastomoses with internal mammary artery or a mean of 3.6 ± 1.0 anastomoses/patient. Sequential grafts were usually used for branches of the same coronary system and occasionally for a secondary branch of a secondary coronary system with 2.2 ± 0.4 distal anastomoses/graft. "Y" grafts were occasionally used with 1.3 ± 0.5 distal anastomoses for each limb. Graft flow rates were measured using an electromagnetic flowmeter just before closure.

Ambulatory electrocardiography: Continuous 2-channel ambulatory ECG recordings (Del Mar Avionics 445) were obtained using bipolar leads CS-aVF and CM-V_5 (95%), or CM-V_1 and CM-V_5 (5%) during daily activity.[16] All amplitude-modulated recordings were calibrated, care was taken to avoid leads with pathologic Q waves and the effects of body postural change were recorded.[16] Diaries of activities, symptoms and ingestion of medications during the ambulatory electrocardiography were obtained. Recordings were analyzed on Del Mar Avionics (models 9000 and 750) instruments for the presence, frequency and duration of ischemic episodes as defined by transient depression of ≥1 mm of J point and ST-segment depression 0.08 second after the J point from the baseline for ≥1-minute duration. If baseline ECG ST-segment depression was present, the criteria required a minimum of an additional 2 mm of J point and ST-segment depression from the baseline. Episodes of ST-segment change were identified by return of the J point and ST-segment to baseline for ≥2 minutes. Because of controversy surrounding the significance of transient ST-segment elevation, patients with only this finding were excluded. All episodes were identified and verified by 2 cardiovascular technicians and a cardiologist by examination of trend ST-segment plots, beat-by-beat printout of miniaturized full-disclosure printouts and standard 25-mm ECG printouts.[16] T-wave changes were not used to diagnose ischemia. All episodes were quantitated in minutes, correlated to diary-indicated sleep, wake activity, and symptoms and classified as being "silent" (asymptomatic) or symptomatic.

Catheterization and angiography: Cardiac catheterization was performed by either the Judkins or Sones technique in a standardized fashion. Angiography allowed visualization of native coronary and vein graft arteriograms obtained in multiple varied orthogonal views recorded at standardized angles on cineangiographic film. If the origin of a vein graft could not be visualized, biplane aortic root angiography was performed. Each angiogram was reviewed independently by 2 cardiologists without knowledge of the patient's randomization or ambulatory ECG findings. The original pre- and postoperative angiogram findings were then confirmed by simultaneous review of the sequential films projected side-by-side at magnification on parallel projectors. Coronary and graft stenoses were considered significant when internal luminal diameter (caliper measured) was narrowed >70% compared with the nearest proximal normal segment. Stenoses >50% were also recorded. Discrepancies were adjudicated by consensus review with 2 cardiologists. Myocardial revascularization was considered angiographically complete according to the following criteria: all proximal sections of major coronary arteries and branches with significant stenoses were grafted, all grafts and anastomotic sites were patent and no significant stenoses distal to graft insertions were detected by angiography.[10]

Follow-up clinical evaluation: All patients were followed prospectively by clinic visit or telephone contact for the occurrence of angina, myocardial infarction, revascularization (percutaneous coronary angioplasty or repeat CABG) and death. Angina was defined as a typical history of chest pain accompanied by objective evi-

TABLE I Clinical Characteristics of Patients Examined Early (1 to 3 Months) and Late (12 Months) After CABG Surgery With and Without Evidence of Silent Ischemia Detected by Ambulatory Electrocardiography

Characteristics	Early After CABG		Late After CABG	
	Silent Ischemia (n = 19)	No Ischemia (n = 67)	Silent Ischemia (n = 50)	No Ischemia (n = 121)
Age (yrs)	58 ± 7	55 ± 8	57 ± 7	55 ± 8
Sex: M/F	18/1	64/3	45/5	111/10
Diabetes (n)	4	21	13	42
Hypertension (n)	4	27	16	47
Current smoking (n)	0	13	9	22
Prior MI (n)	12	45	28	77
Calcium antagonists (n)	0	0	3	7
β blockers (n)	4	13	12	20
Nitrates (n)	0	3	5	2*
Antiplatelet therapy (n)	11	38	24	62
Mean cholesterol (mg/dl)	229 ± 37†	222 ± 34†	238 ± 53	228 ± 43
Mean triglycerides (mg/dl)	214 ± 99†	224 ± 111†	238 ± 110	234 ± 146
Angina before CABG (n)				
Class I to II	4	21	15	30
Class III to IV	15	46	35	91
Angina after CABG (n)				
Class I to II	1	7	2	6
Class III to IV	1	3	3	2

* $p < 0.05$; † measured before surgery.
CABG = coronary artery bypass grafting; MI = myocardial infarction.

TABLE II Characteristics of 24-Hour Ambulatory Electrocardiographic ST-Segment Depression Episodes Detected in 19 Patients Early (1 to 3 Months) and 50 Patients Late (12 Months) After CABG

Patient Group	No. of Total Episodes	Episodes/Pt*	Total Ischemic Duration (minutes)	Duration/Pt* (minutes)	Duration/Episode† (minutes)
Early after CABG (n = 19)					
Silent	199	10 ± 9	3,055	161 ± 171	15 ± 2
Symptomatic	2	1 ± 0	45	22 ± 2	22 ± 2
Late after CABG (n = 50)					
Silent	292	6 ± 5	8,277	166 ± 240	23 ± 3
Symptomatic	2	2 ± 0	44	44 ± 0	22 ± 8

* Data are mean ± standard deviation; † data are mean ± standard error of the mean.
CABG = coronary artery bypass grafting.

dence of ECG ST-segment changes or radionuclide changes. Angina class was established by the Canadian classification. Myocardial infarction was defined by prolonged chest pain with associated ECG changes and elevated cardiac enzymes. The decision for repeat revascularization was made by the referring physicians, and depended on evidence of increasing myocardial ischemia unresponsive to an adequate medical regimen. All circumstances of death were verified by direct contact with family members and the primary physician.

Data analysis: Continuous variables were analyzed using the paired and unpaired Student *t* tests. Chi-square tests were applied to categorical data. Because proximal occlusion of a sequential or Y-branched graft usually results in occlusion of all downstream distal anastomoses, observations made on distal anastomoses in these grafts are not truly independent, and standard statistical tests do not apply. Similarly, multiple grafts in a patient are not independent. Thus, patency data were analyzed 3 ways according to Goldman et al[17]: (1) by comparison of grafts that were occluded, assuming grafts were not independent, (2) by comparison of grafts that were occluded, assuming each graft was independent and (3) by comparison of the proportion of patients with ≥1 occluded graft.

To analyze time-to-event data with censored observations, life-tables of the survival of early and late CABG patients were obtained using the product-limit Kaplan-Meier method with Breslow and Mantel-Cox statistics to compare the survival equality of patients with and without ST-segment depression.[18] Further analyses of survival data were based on fitting Cox proportional-hazards regression models (BMDP-2L computer program)[19] to study the influence of several covariates on time-to-event. Covariates included age, sex, noninsulin-dependent diabetes, hypertension, current smoking, history of prior myocardial infarction, cardiac medications, antiplatelet therapy, mean cholesterol and triglycerides, angina class, extent of coronary artery disease (number of major coronary arteries with >70% stenoses), ejection fraction, number of grafts, number of anastomotic sites, number of grafts occluded/patient, number of anastomotic sites occluded/patient, number of grafted arteries with distal stenosis (70 and 50%),

number of ungrafted native arteries with significant stenosis (70 and 50%), ventricular wall motion score, New York Heart Association class (before CABG), presence of ST-segment depression and total ischemic duration (<30, 30 to 60 and >60 minutes). Statistical significance was accepted at $p < 0.05$.

RESULTS

Clinical characteristics: Ambulatory ECG examination of the 94 patients examined early after CABG detected 19 (20%) patients with transient ST depression, 8 (9%) patients with transient ST elevation and 67 (71%) patients without ST-segment changes. Similarly, of 184 patients examined late after CABG, 50 (27%) patients showed transient ST depression, 13 (7%) patients showed transient ST elevation and 121 (66%) patients had no ST-segment changes. All patients with ST-segment depression were asymptomatic, with the exception of 2 patients in the early group, and 1 patient in the late group who also had typical angina.

The clinical characteristics of 86 early and 171 late patients with and without silent ischemia detected after CABG are listed in Table I. No significant differences were found between patients with or without silent ischemia except for the increased use of nitrates in silent ischemia patients in the late group. Significantly ($p < 0.05$) reduced angina occurred in all patients after CABG, and no differences existed between patients with and without silent ischemia (Table I). Antiplatelet therapy was equally distributed among patients with and without silent ischemia.

Ambulatory electrocardiography: Ambulatory electrocardiography in 86 early patients (total 1,880 hours, mean 22 ± 2 hours) and in 171 late patients (total 3,680 hours, mean 22 ± 2 hours) detected transient ST depression in 69 of the 257 (27%) examinations. Characteristics of the ischemic episodes found in 19 early and 50 late patients are listed in Table II. Two of 5 early patients and 5 of 13 late patients had persistent baseline ST-segment depression and episodes of ST-segment depression >2 mm over baseline. Analysis of the data with or without inclusion of these patients was not significantly different, and their findings were included. Virtually all episodes (99%) of transient ST-segment depression detected were asymptomatic.

The circadian distribution of the time of occurrence of number of episodes and minutes of ischemic duration are listed in Figure 1. The frequency of ischemic episodes significantly peaked in the morning hours between 6 A.M. and 12 noon, and a second modal peak was observed between 6 P.M. and midnight in patients both early and late after CABG (analysis of variance: early, p =

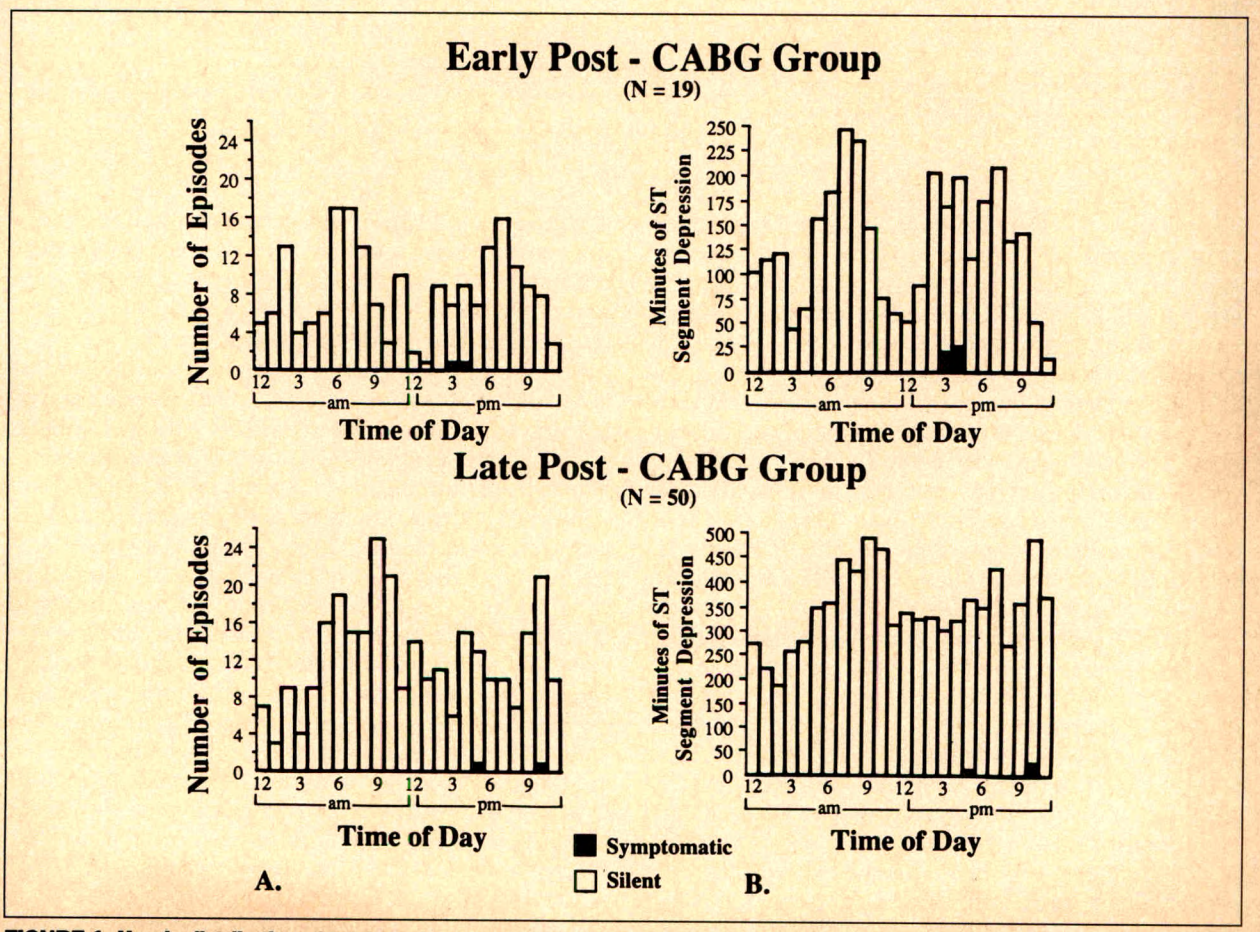


FIGURE 1. Hourly distribution of total number of episodes (*A*) and total minutes of ST-segment depression (*B*) detected in 19 patients examined early (1 to 3 months) and 50 patients examined late (12 months) after coronary artery bypass grafting (CABG).

TABLE III Angiographic and Hemodynamic Characteristics of Patients Examined Early (1 to 3 Months) and Late (12 Months) After CABG With and Without Evidence of Silent Ischemia Detected by Ambulatory Electrocardiography

Characteristics	Early After CABG		Late After CABG	
	Silent Ischemia (n = 19)	No Ischemia (n = 67)	Silent Ischemia (n = 50)	No Ischemia (n = 121)
No. of vessels with >70% stenosis*				
1	2	10	5	13
2	6	33	25	47
3	11	24	20	59
Left main ≥50%	2	5	7	20
No. of grafts				
0 SVG	1	11	8	12
1 SVG	12	32	28	48‡
2 SVG	5	21	9	51§
3 SVG	1	2	5	8
4 SVG	0	1	0	2
1 Seq	9	33	27	54
2 Seq	2	9	4	7
1 Y	2	5	6	6
1 IMA	7	18	16	41
2 IMA	0	2	1	4
1 IMA Seq	2	11	6	20
Mean grafts/pt	2.7 ± 1.0	2.7 ± 0.7	2.6 ± 0.7	2.7 ± 0.6
Mean anastomotic sites/pt	3.6 ± 0.8	3.7 ± 1.0	3.6 ± 1.0	3.6 ± 1.0
EF before CABG†	66 ± 12	64 ± 16	64 ± 15	66 ± 15
EF after CABG	68 ± 14	67 ± 14	64 ± 14	65 ± 13
No. of patients				
EF ≥40	17	60	48	117
EF <40	0	2	2	4
LVEDP (mm Hg) before CABG	13 ± 5	13 ± 7	13 ± 8	12 ± 6
LVEDP (mm Hg) after CABG	10 ± 5	11 ± 6	11 ± 5	11 ± 4

* Left main disease included as 2-vessel disease, and 2 patients missing in the group late after CABG because of 50% stenosis; † not all patients had EF; ‡ $p < 0.05$; § $p < 0.001$. CABG = coronary artery bypass grafting; EF = ejection fraction; IMA = internal mammary artery implant; LVEDP = left ventricular end diastolic pressure; Seq = sequential vein graft; SVG = isolated saphenous vein graft; Y = Y-graft (2 limbs).

0.018; late, $p = 0.001$) (Figure 1A). Significant differences occurred for frequency of episodes between the period of 6 A.M. to 12 noon (early group $p < 0.05$, late group $p < 0.001$) and the period of 6 P.M. to midnight (early and late group $p < 0.05$). Similarly, total ischemic duration also had a peak distribution between 6 A.M. and 12 noon for both groups, but did not achieve statistical significance (Figure 1B). Examining minutes of ST-segment depression after awakening showed that the first hour of wake activity demonstrated maximal ischemic duration compared to any other hour. One quarter of all ischemic duration occurred in the initial 3 hours of wake activity in both groups (early 847 minutes, late 1,678 minutes; $p < 0.01$).

Cardiac catheterization: Cardiac catheterization was performed a mean of 1.7 ± 0.6 (range 0.8 to 3.8) months after CABG in the early group, and a mean of 12.3 ± 1.3 (range 11 to 22) months in the late group. Ambulatory electrocardiography was obtained after catheterization within 1 week in 67% (early 14, late 156), within 1 month in 75% (early 21, late 168) and within 3 months in 100% (early 86, late 171) of patients. Multivessel coronary disease (early 86%, late 89%) did not significantly differ in patients with or without silent ischemia (Table III). Relatively more patients with 1 vein graft and fewer patients with 2 vein grafts occurred in patients with silent ischemia in the late group ($p < 0.05$). The distribution of grafts, ejection fractions or mean ejection fraction and end-diastolic pressure before and after CABG failed to show significant differences (Table III). Overall, good left ventricular function dominated both patient groups.

Graft and anastomotic site patency and the number of patients with graft or site occlusions revealed no significant differences between patients with and without silent ischemia (Table IV). Grafted arteries with residual distal significant stenosis and ungrafted arteries with significant stenoses also failed to show significant differences, although the early group did show a greater percent of ungrafted arteries in patients with silent ischemia (58 vs 36%) (Table IV). The addition of data to include >50% stenosis to both groups also failed to disclose any significant differences. Complete revascularization was unrelated to the absence of silent ischemia (Table IV). Moreover, examination of saphenous vein and internal mammary artery graft flow rates measured at the time of CABG indicated no propensity for low bypass graft flow (<40 ml/min) in patients with silent ischemia, although it was apparent that the greatest percent of graft or anastomotic site occlusions occurred at low graft flow rates ($p < 0.01$) (Table V).

Long-term follow-up: Follow-up data were available for 97% (83 of 86) of early patients and 96% (165 of 171) of late patients. During 62 months (mean 48 ±

TABLE IV Angiographic Graft, Anastomotic Site and Native Vessel Patency in Patients Examined Early (1 to 3 Months) and Late (12 Months) After CABG With and Without Evidence of Silent Ischemia Detected by Ambulatory Electrocardiography

	Early After CABG		Late After CABG	
	Silent Ischemia (n = 19)	No Ischemia (n = 67)	Silent Ischemia (n = 50)	No Ischemia (n = 121)
Graft patency (%)†	40/42 (95)	137/145 (94)	98/107 (92)	239/262 (91)
Anastomotic site patency (%)†	51/57 (89)	193/207 (93)	130/150 (87)	304/347 (88)
Patients with graft occlusions (%)†	2 (11)	7 (10)	10 (20)	21 (17)
Patients with site occlusions (%)†	4 (21)	11 (16)	13 (26)	30 (25)
Grafted vessels with >70% distal stenosis (%)	5/42 (12)	17/145 (12)	11/107 (10)	38/262 (15)
Patients with >70% stenosis of ungrafted vessels (%)	11 (58)	24 (36)	22 (44)	50 (41)
Patients completely revascularized (%)	6 (32)	33 (49)	19 (38)	48 (40)

† only saphenous vein grafts assumed to be independent.
CABG = coronary artery bypass grafting.

TABLE V Saphenous Vein and IMA Graft Flow Rates in Grafts of Patients Examined Early and Late After CABG With and Without Evidence of Ambulatory Electrocardiography Silent Ischemia

	Early After CABG				Late After CABG			
	Silent Ischemia (n = 19)		No Ischemia (n = 67)		Silent Ischemia (n = 50)		No Ischemia (n = 121)	
	Graft Occlusions	Site Occlusions	Graft Occlusions	Site Occlusions	Graft Occlusions	Site Occlusions	Graft Occlusions	Site Occlusions
Vein graft flow								
<40 ml/min	1/8 (13)	2/10 (20)	4/31 (13)	4/37 (11)	6/28 (21)	7/31 (23)	13/53 (25)	16/65 (25)
40–80 ml/min	1/17 (6)	4/23 (17)	2/70 (3)	6/103 (6)	3/48 (6)	10/72 (14)	7/142 (5)	17/177 (10)
>80 ml/min	0/14 (0)	0/21 (0)	2/40 (5)	5/66 (8)	0/26 (0)	3/46 (7)	3/67 (4)	9/104 (9)
Total	2/39 (5)	6/54 (11)	8/141 (6)	15/206 (7)	5/102 (5)	20/149 (13)	23/262 (9)	42/346 (12)
IMA graft flow								
<40 ml/min	0/6 (0)	0/7 (0)	0/19 (0)	0/24 (0)	0/18 (0)	0/21 (0)	1/43 (2)	3/51 (6)
40–80 ml/min	0/3 (0)	0/4 (0)	0/13 (0)	0/18 (0)	0/5 (0)	0/7 (0)	0/20 (0)	2/32 (6)
>80 ml/min	— —	— —	0/1 (0)	0/2 (0)	0/1 (0)	0/2 (0)	0/2 (0)	0/2 (0)
Total	0/9 (0)	0/11 (0)	0/33 (0)	0/44 (0)	0/24 (0)	0/30 (0)	1/65 (2)	5/85 (6)

Measurements were obtained in 97% (538 of 556) of all vein grafts and 100% (131 of 131) of internal mammary artery implants.
CABG = coronary bypass grafting; IMA = internal mammary artery.
Numbers in parentheses are percent of patients.

11) of follow-up, 18 early patients and 25 late patients sustained a clinical event (Table VI). Chi-square or Kaplan-Meier analysis showed no significant differences in events between patients with or without silent ischemia in either group (Table VI, Figure 2). Breslow and Mantel-Cox testing did not reject equality of survival (early, p = 0.19 and 0.15, late, p = 0.77 and 0.72). Kaplan-Meier analysis of clinical events only during the first year after CABG, excluding patients with angina as an endpoint or only for patients who demonstrated <30, 30 to 60 and >60 minutes of total ischemic duration, again showed no association of silent ischemia to increased risk of an adverse outcome. Adding patients with ST-segment elevation only (early, 8 patients—no events; late, 13 patients—1 revascularized, 2 angina) to the early and late groups did not influence outcome. To exclude selection bias of the early group, the survival of the 113 patients examined 1 month during hospitalization and not reexamined as outpatients, was compared to the early group. Twenty-one adverse clinical events occurred in the former group and Kaplan-Meier survival analysis disclosed no difference compared to the early group.

Stepwise Cox regression models were applied to clinical and angiographic variables of patients examined early and late after CABG. For the early group, only increased age (regression coefficient = −0.056, p = 0.03) indicated a mildly positive relation with freedom from cardiac events (relative risk 1.06 [95% confidence interval, 1.01 to 2.94]). Although ejection fraction was not a significant predictor, after age entered the model in a stepwise fashion, it approached significance (p = 0.10). In patients examined late after CABG, no variable was related independently to outcome.

DISCUSSION

Ambulatory electrocardiographic silent ischemia: We used ambulatory electrocardiography to assess silent myocardial ischemia, and found transient ST-segment depression in 20% of patients 1 to 3 months and in

TABLE VI Clinical Outcome of Patients With and Without Silent Ischemia Detected Early and Late After CABG

Adverse Clinical Event	Early After CABG		Late After CABG	
	Silent Ischemia (n = 19)	No Ischemia (n = 67)	Silent Ischemia (n = 50)	No Ischemia (n = 121)
Myocardial infarction	0	2	0	3
CABG/PTCA	1	2	2	3
Cardiac death	0	1	0	2
Sudden death	0	1	0	1
Angina	1	8	3	6
Noncardiac death	0	2	2	3

CABG = coronary artery bypass grafting; PTCA = percutaneous transluminal coronary angioplasty.

27% of patients 12 months after CABG. These findings are consistent with the 15 to 33% prevalence of silent ischemia detected by other studies that used 24- to 36-hour ambulatory electrocardiography in patients 3 to 5 months after CABG.[8–11] Whereas virtually all episodes (99%) of transient ST-segment depression detected in the present groups were silent or asymptomatic, symptomatic angina has been described in 7 to 22% of patients examined 3 months after CABG in smaller studies.[8–10] Characteristics of silent ischemia in this study were similar to those previously described for patients with chronic stable angina[2,20–22] or after CABG.[8] Frequency of episodes ranged from a mean of 6 to 10 episodes/24 hours, with a mean duration of 15 to 23 minutes. The circadian distribution of episodes of silent ischemia disclosed a significant occurrence in the period between 6 A.M. and 12 noon and a secondary peak between 6 P.M. and midnight ($p < 0.01$ and $p < 0.001$). Increased ischemic duration between 6 A.M. and noon also approached statistical significance, and clearly the initial hour after awakening harbored the maximum ischemic duration for most patients. These circadian patterns are consistent with other patients with stable coronary artery disease.[3,23,24]

Relation of silent ischemia to completeness of revascularization: Relief of angina pectoris and improvement of exercise capacity often occur after CABG, but

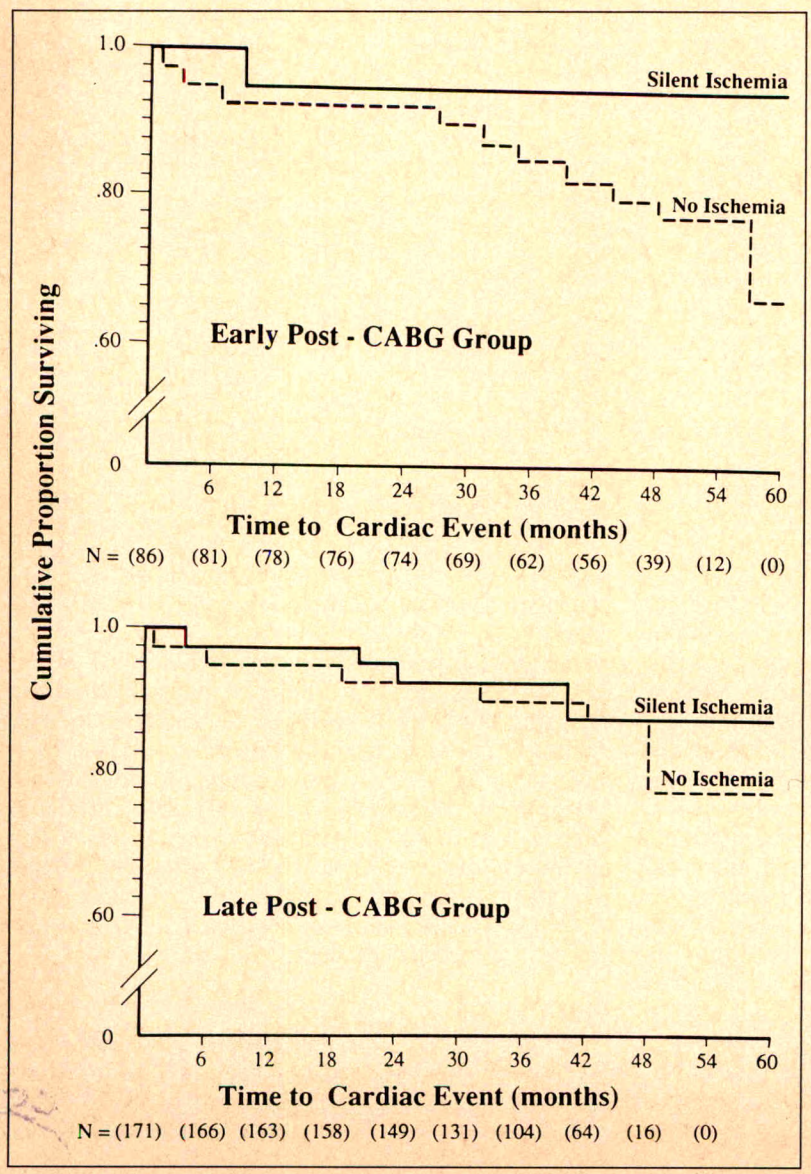


FIGURE 2. Kaplan-Meier analysis of time to adverse cardiac event (angina, myocardial infarction, coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty, and cardiac or sudden death) in patients with silent ischemia and no ischemia as detected by ambulatory electrocardiography in 86 patients examined early (*top*) and in 171 patients examined late (*bottom*) after CABG and followed prospectively. No statistical differences were found. N = number of patients at follow-up.

do not necessarily correlate with graft patency or normalization of electrocardiography on exercise testing.[8,10–13] Even when graft patency is established as the "gold standard", it is not necessarily indicative of physiologic relief of transient myocardial ischemia. Ribeiro et al,[8] using regional myocardial perfusion positron tomography and ambulatory electrocardiography, have shown that CABG relieves symptoms by 3 different mechanisms—relief of transient ischemia, perioperative myocardial infarction and conversion of angina pectoris to silent myocardial ischemia. The latter study documented that 3 of 15 patients lost their angina and had patent grafts, but showed reversible transient abnormalities of myocardial perfusion and silent ischemia during exercise testing and ambulatory electrocardiography.[8] The investigators speculated that these abnormalities resulted from coronary stenoses distal to the graft insertion, low graft flow rates or abnormal extravascular or intravascular resistance distal to the graft.[8] Other investigators have confirmed transient myocardial ischemia and patent grafts in patients after CABG, and have implicated distal stenotic disease in grafted vessels or other ungrafted native vessels.[9] Rarely, coronary vasospasm with ST-segment depression and elevation is invoked as the etiologic mechanism after CABG.[10]

We extend and confirm previous data. The present study documents an equal graft and anastomotic site patency rate in patients with and without silent ischemia both early and late after CABG, and confirms reports of improved early and late graft patency with antiplatelet therapy.[14,15,17] Examination of significant coronary stenoses distal to the graft insertion, ungrafted stenotic native vessels or low graft flow rates measured at the time of surgery were unrelated to silent ischemia (Tables IV and V). Adding data relative to the presence of >50% stenoses to both study groups also failed to show a statistically significant difference between patients with and without silent ischemia.

The dominant etiology of the silent ischemia in the present study remains speculative. Whereas other investigators have documented that disturbed regional myocardial perfusion accompanies episodes of transient ST-segment depression detected after CABG,[8] these data seem to exclude angiographic definable stenotic vessels as the dominant mechanism in the early years after CABG. Perhaps presurgical abnormalities of elevated coronary vascular resistance or acquired abnormal vasodilatory coronary flow reserve of the microcirculation due to endothelial or prearteriolar abnormalities after CABG, or both, account for the silent ischemia.[25,26] Egstrup[11] demonstrated in 12 of 36 patients examined by ambulatory electrocardiography before and after CABG that some individuals increased ischemic activity (episodes and duration), and were asymptomatic or had minimal symptoms.

Relation of silent ischemia to prognosis: The prognostic merit of ambulatory ECG silent ischemia in coronary artery disease patients has been demonstrated.[1,4,27–29] Ambulatory ECG silent ischemia detected after CABG was reported to be the most powerful predictor of cardiac events during a 9-month follow-up period as compared to 10 different clinical variables.[11] In contrast, during 62 (mean 48 ± 11) months of follow-up we found no association between silent ischemia and adverse clinical events. When the analysis was confined to events only within the initial 12 months of follow-up, excluding angina, or to patients with varying ischemic durations, there continued to be no significant relation found. Moreover, the Cox multivariate analysis of 30 clinical, angiographic or hemodynamic covariates on the time-to-event showed only a minimal increased relative risk (1.06) associated with younger age in the early group. Reasons for these differing findings are unclear. Certainly, our study differs in that we assessed larger groups of patients (86 and 171 vs 36), and our patients were consecutively entered (not selected), experienced fewer events after CABG and had overall good left ventricular function. We used 24-hour (not 36-hour) ambulatory electrocardiography.[11] A host of other factors, however, including clinical variables analyzed by Cox stepwise regression technique, were similar.[11] These findings are similar to those of Erickssen,[30] who found (during follow-up of asymptomatic patients with and without exercise-induced ST depression) more clinical events occurring in patients without ST depression.

Study limitations: Selective factors of the clinical trial protocol and the entry time period contributed to a dominance of good left ventricular function observed in the study groups. These observations should only be generalized to such patients. Because few adverse clinical events occurred during follow-up, we calculated a power of 90 and 85% (type II error 10 and 15%) to detect a difference of 50 and 30% reduction, respectively, in the survival of patients with silent ischemia in the late group.[31] However, the low event rate experienced in the early group precluded a low type II error. Nonetheless, good ventricular function and antiplatelet therapy (now standard practice) may have selected low-risk CABG patients, and our study sample may be too small to reveal weak differences (10 or 20%) in patients with silent ischemia.

Clinical implications: We confirm that CABG relieves angina in most patients, but evidence of ambulatory ECG silent ischemia persists in 20 to 30% of patients 1 to 3 months and 12 months after CABG. This silent ischemia was not significantly associated with increased bypass graft or anastomotic site occlusion, low graft flow rates measured at the time of surgery, distal stenotic disease in grafted arteries or the presence of other stenotic ungrafted native arteries in the present study. Prospective follow-up of CABG patients with relatively good ventricular function suggests ambulatory ECG silent ischemia has little, if any, increased risk of an adverse clinical outcome in the early years after CABG.

Acknowledgment: We gratefully acknowledge the expert secretarial assistance of Linda Benson and Kathleen Collins, and the art assistance of Deborah Brown.

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Frequency and Significance of Late Evolution of Q Waves in Patients with Initial Non-Q-Wave Acute Myocardial Infarction

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Serial 12-lead electrocardiogram and plasma creatine kinase (CK)-MB values from 544 patients with confirmed non-Q-wave acute myocardial infarction (AMI) were analyzed to define the rate of progression of non-Q-wave AMI to Q-wave AMI and to examine its relation to CK-MB evidence of extension. The baseline electrocardiogram was obtained 50 ± 10 hours after AMI and compared with subsequent electrocardiograms at 48 and 72 hours after baseline record and at discharge. Plasma CK-MB was assayed every 12 hours after baseline. A total of 76 patients (14%) progressed to Q-wave AMI. Compared to the 468 patients who retained non-Q-wave AMI, those patients who evolved Q-wave AMI were more likely to exhibit ST elevation ≥1.0 mm in ≥2 infarct-related leads (49 vs 32%, p <0.005), higher peak CK values with the index AMI (754 ± 625 vs 611 ± 604 IU; p = 0.0018) and a greater incidence of CK-MB-confirmed extensions (18.5 vs 5.5%, p <0.0001). For those patients progressing to Q-wave AMI within 48 hours of baseline electrocardiogram, CK-MB extension occurred in 9.5% (4 of 42) versus 29.4% (10 of 34) of those who progressed after 48 hours (p = 0.0262). A distinct minority (14%) of patients with non-Q-wave AMI will develop Q waves before discharge. The progression to Q-wave AMI after initial non-Q-wave AMI appears to involve 2 different mechanisms: temporal lag in the electrocardiogram, and actual extension by quantitative CK-MB criteria.

(Am J Cardiol 1990;65:23–27)

During the last decade, important clinical and prognostic differences between Q-wave and non-Q-wave acute myocardial infarction (AMI) patients have emerged.[1–7] Compared to patients with Q-wave infarction, patients with non-Q-wave AMI have smaller infarct size, better residual left ventricular function and lower in-hospital mortality.[8–11] Long-term survival after non-Q-wave AMI, however, appears to be similar to or even less than that in patients with Q-wave AMI.[5,11,12,15] Several investigators have shown that the incidence of angina after infarction,[13–14] the rate of recurrent infarction[15–19] and possibly the risk of sudden death[3] are higher after an initial non-Q-wave AMI. This suggests that non-Q-wave AMI events represent incomplete infarction and may be a harbinger of greater clinical instability caused by the presence of a larger residual mass of viable but jeopardized myocardium within the perfusion zone of the infarct-related vessel.[11,15,19]

We used the extensive clinical and laboratory information from a large cohort of patients with isoenzyme-confirmed non-Q-wave AMI contained in the database created for the Diltiazem Reinfarction Study. Our current objective was to examine prospectively the sequential electrocardiograms of 576 randomized patients to determine the proportion of non-Q-wave AMI patients who evolved Q-wave AMI before hospital discharge; to assess the time course of such Q-wave development; to correlate the clinical, enzymatic and outcome differences between subgroups of non-Q-wave AMI patients who did or did not develop Q-wave AMI during hospitalization; and to determine the mechanism or mechanisms for late development of Q waves. We expected that the 2 major mechanisms would be reinfarction with development of new Q waves and temporal delay between the initial pathologic event and the electrocardiographic development of Q waves, which we have called "electrocardiographic lag."

METHODS

The Diltiazem Reinfarction Study database, which was developed from 1982 to 1985, contains information on 576 consenting patients with creatine kinase (CK)-MB–confirmed non-Q-wave AMI who were randomly assigned to receive treatment with either diltiazem (287) or placebo (289) in addition to standard medical therapy. Each patient satisfied inclusion and exclusion criteria, and began receiving study medication 53 ± 14

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TABLE I Clinical Findings in the 544 Patients

	Development of Q Waves (n = 76)	p Value	NQMI only (n = 468)
Peak creatine kinase	754 ± 579	0.0193	604 ± 676
Age (yrs)	60 ± 9	NS	61 ± 10
ST elevation (%)	37/76 (40)	0.037	150/468 (32)
ST depression (%)	46/76 (61)	NS	241/468 (52)
T-wave inversion (%)	39/76 (51)	NS	272/468 (58)

NQMI = non-Q-wave myocardial infarction; NS = not significant.

hours (range 24 to 72) after the onset of AMI. Complete details of the organization and conduct of the trial, as well as baseline characteristics of patients according to treatment group assignment, have been reported.[20]

Clinical and laboratory evaluation: After randomization, the following evaluations were performed: (1) daily clinical evaluation by the investigator; (2) 12-lead electrocardiogram on enrollment and daily for the first 5 days, followed by every other day thereafter until 14 days or hospital discharge; (3) electrocardiogram at the time of recurrent pain and for a minimum of 3 consecutive days if reinfarction was suspected; and (4) serial blood samples for analysis of total and CK-MB activity. All protocol samples were forwarded to the CK core laboratory for quantitative analysis of plasma CK-MB activity by the batch adsorption glass bead method.[21,22] Sampling times consisted of an initial sample at the time of randomization, followed by samples drawn every 12 hours thereafter throughout the 14-day study. Additional samples were obtained at least every 8 hours for the subsequent 72 hours in patients in whom reinfarction was suspected.

The primary endpoint of the Diltiazem Research Study[20] was reinfarction during the 14-day study period. This was defined as an increase of ≥50% in plasma CK-MB activity above baseline (mean of 2 preceding samples) in ≥2 samples separated by a minimum of 6 hours within a 24-hour interval, with an absolute value of ≥14 IU/liter in at least 1 sample. Based on previous studies with this assay, the normal range of plasma CK-MB is 0 to 13 IU/liter.[22]

Treatment regimen: The treatment regimen for study and placebo patients has been described.[20] Other than study drugs, therapy was conventional except concurrent treatment with calcium antagonists was prohibited.

Electrocardiographic analyses: Four sequential electrocardiograms from each of the 576 randomized patients were analyzed by 5 blinded investigators, who entered these data on forms for subsequent computer analysis. Serial tracings at entry into the trial (prestudy), on study day 2, study day 3 and predischarge were analyzed. A total of 2,263 electrocardiograms were available for review. The mean time of the prestudy electrocardiogram was 50 ± 10 hours after onset of AMI, and for the predischarge electrocardiogram was 11.0 ± 3.5 days. The predischarge tracing was available after day 3 for 93% (535 of 576) of patients.

Patients included in the study were defined electrocardiographically by the absence of abnormal Q waves (i.e., ≥0.03 seconds in duration in 2 leads within a given lead group or the absence of R waves ≥0.04 second in lead V_1 and an R:S ratio ≥1 in lead V_2). Thirty-two patients had pathologic Q or R waves on entry to the study and these patients were censored from this analysis.

Acute ST-segment displacement or T-wave inversions were not prerequisites for entry in the study. Significant ST-segment shifts were defined as the presence of ≥1 mm of ST-segment elevation, depression or T-wave inversion (or, in the presence of left ventricular hypertrophy, ≥2 mm of ST-segment depression) in ≥2 leads within a given non-Q-wave AMI location: anterior = V_1–V_4; lateral = I, aVL, V_5–V_6; inferior = II, III, aVF. Electrocardiographic localization of non-Q-wave AMI (or progression to Q-wave AMI) required that indicative changes be observed in ≥2 leads within an infarct location.

Definition of outcome variables: In addition to the primary endpoint of enzymatic reinfarction during the 14-day treatment period, a variety of other outcome variables were analyzed, including the development of Q-waves, postinfarction angina, angina with electrocardiographic changes and mortality. To assess more carefully the relation between diltiazem treatment assignment and the development of Q waves, matched pairs were defined in the following way: each patient who developed pathologic Q waves was matched with a patient who did not. The matching process was designed to ensure that both members of every pair experienced CK-MB reinfarction (11) or both members did not reinfarct (62); and the members of each pair had similar peak CK values. The total number of matched pairs was 73 because adequate matches could not be found for 3 of the 76 patients who developed Q waves. The patients in these matched pairs were analyzed according to a variety of selected clinical and laboratory outcome variables including age, sex, obesity, smoking history, prior myocardial infarction, Killip class, use of concomitant β blocker and nitrate therapy, the presence of associated ST-segment elevation or depression or T-wave inversion, or both, postinfarction angina with and without electrocardiogram changes and left ventricular hypertrophy by electrocardiogram.

Statistics: All data were analyzed using the Washington University IBM mainframe computer system. Results are expressed as mean ± standard deviation. Because of the skewed nature of the variable, all analyses that involved peak CK were performed after logarithmic transformation. Moreover, to ensure comparability of all CK measurements, adjustments were made in the raw CK values. These adjustments accounted for the varying definitions of maximum normal CK among the participants in the Diltiazem Reinfarction Study. The means of continuous variables were compared using *t* tests, whereas all 2 × 2 contingency tables were analyzed using chi-square tests. The relation between progression to Q-wave AMI and diltiazem was assesed through the use of matched pairs. Each patient who progressed to Q-wave AMI was paired with 1 patient who did not. The matching was accomplished in a fashion that ensured that both members of each pair were

TABLE II Baseline Electrocardiographic Findings for the 76 Patients Who Developed Q Waves

Q-Wave Location	Anterior				Lateral				Inferior			
	TC	ST↑	ST↓	T↓	TC	ST↑	ST↓	T↓	TC	ST↑	ST↓	T↓
A (n = 19)	18	9	6	6	11	0	7	9	5	3	1	2
AL (n = 1)	1	0	0	1	0	0	0	0	0	0	0	0
L (n = 6)	4	3	1	0	5	1	3	2	2	0	1	2
IL (n = 1)	1	1	0	0	1	1	0	0	1	1	0	1
I (n = 26)	13	7	6	1	18	0	14	13	16	9	2	7
IP (n = 3)	2	0	2	1	2	0	2	0	3	2	1	1
P (n = 20)	13	1	12	2	10	2	6	3	8	4	3	3

A = anterior; AL = anterolateral; I = inferior; IL = inferolateral; IP = inferoposterior; L = lateral; P = posterior; TC = total no. of patients with ST and/or T abnormalities (total changes).

concordant with respect to the presence or absence of extension and the magnitude of peak CK. Because of this pairing, contingency table analyses that compared progression to Q-wave AMI with the use of diltiazem or with any other dichotomous variable were automatically adjusted for both extension and peak CK. Because the data were paired, McNemars test[23] was used to analyze the contingency tables.

RESULTS

Table I lists the electrocardiographic, clinical and demographic findings in the 544 patients with non-Q-wave AMI. Seventy-six of the 544 patients (14%) evolved Q-wave AMI subsequent to the qualifying electrocardiogram based on a review of serial tracings.

Table I also compares electrocardiographic, demographic and clinical variables found on presentation of the 76 patients who developed Q waves and the 468 patients who did not. Patients who developed Q waves had significantly higher CK levels (754 vs 604 IU, $p < 0.001$), and significantly more ST elevation on presentation (48.7 vs 32.1%, $p = 0.037$). No significant between-group difference was found in age, presence of T inversion or ST depression.

Although ST elevation was significantly increased in patients who developed Q waves ($p = 0.037$), 51% in this group did not exhibit ST elevation. Conversely, nearly a third of patients who did not develop Q waves had ST elevation. Thus, ST elevation was neither sensitive (49%) nor specific (20%) for the development of Q waves, and accordingly, the predictive value was low.

Table II lists the location of the Q waves in the 76 patients who developed Q waves after randomization to study and tabulates the electrocardiographic findings they had at presentation before they developed Q waves. There was a total of 20 anterior infarcts (19 anterior in a single location and 1 anterolateral); a total of 8 lateral infarcts (6 lateral, 1 anterolateral and 1 inferolateral); a total of 30 inferior (26 inferior, 1 inferolateral and 3 inferoposterior); and a total of 23 posterior (20 posterior and 3 inferoposterior). Thus, the numerical sum of anterior, inferior and posterior infarcts was 81 because Q waves in 5 patients developed in 2 locations. From the tabulation of changes it can be seen that 19 of 20 patients who developed anterior Q waves presented with anterior ST or T-wave abnormalities, or both. More than half of these patients had changes in the lateral leads, predominantly ST depression and T inversion. Only a quarter had inferior abnormalities. The inferior ST elevation and T inversion changes were not reciprocal in nature.

Of the 8 lateral infarcts, 6 had ST-segment or T abnormalities in the lateral leads, predominantly ST depression, T inversion, or both. The same number had such changes in the anterior leads as well, but only 3 had inferior changes and 1 of these developed Q waves inferiorly as well as laterally.

The 30 patients who developed inferior Q waves showed an interesting pattern. Two-thirds had changes in the inferior leads, mostly ST elevation and T inversion but 21 also had changes in the lateral leads, predominantly ST depression and T inversion, which may have been reciprocal. Sixteen of the 30 had anterior changes that were evenly divided between ST elevation and ST depression.

Of the 23 patients who developed pathologic R waves (posterior infarction) 14 (61%) had anterior ST depression. About half of these patients also presented with either lateral or inferior changes, or both. It can be seen from this summary that posterior infarcts were characterized by a much higher proportion of patients with anterior ST depression than were anterior infarcts (14 of 23 vs 6 of 20). Irrespective of where Q waves or pathologic R waves developed, abnormalities of ST segments and T waves were found in other lead areas. Most of these changes were not reciprocal in nature because marked ST elevation was not a prominent feature of our patient population because initial Q-wave infarcts were excluded.

Development of Q waves and extension by creatine kinase analysis: Of the 76 patients who developed Q waves only 14 (18%) also had infarct extensions established by secondary increases in CK-MB. Seven of the patients (50%) developed Q waves and enzymatic extension within 48 hours of each other. In 3 patients, the Q-wave and CK-MB–confirmed determined extension occurred more than 48 hours apart, and in the remaining 6, data were insufficient to correlate the 2 events. The late development of Q waves had a significantly higher association with CK extension, but even in those patients who developed late Q waves (study day 3 or later), the majority did not exhibit CK-confirmed extensions. These data show a significantly higher rate of isoenzyme-confirmed extension in the group that evolved Q waves (14 of 176 = 18.4%) compared to the non-Q group who did not (28 of 468 = 5.6%, $p = 0.008$).

To assess more carefully the relation between diltiazem and progression to Q-wave AMI in the 76 study patients who evolved Q waves, each patient who progressed to Q-wave AMI was paired with 1 patient who did not progress according to the presence or absence of extension and similar peak CK data on the index infarction. This produced 11 matched pairs of patients who extended (peak CK of 428 ± 192 IU in the Q-wave progression subgroup vs 418 ± 197 IU in the Q-wave non-progression subgroup), and 62 pairs of patients who did not extend (peak CK of 789 ± 557 IU in the Q-wave progression subgroup vs 789 ± 557 IU in the non-progression subgroup). Because this pairing produced similarity between groups who did and did not exhibit extension by quantitative CK-MB criteria, all of the analyses were automatically statistically adjusted for the 2 variables. Although diltiazem significantly reduced infarct extension, McNemars test indicated that diltiazem did not prevent progression to Q-wave myocardial infarction. A similar analysis of the 73 matched pairs showed no relation between progression to Q-wave AMI and gender, Killip class, obesity, use of β blockers or nitrates, presence of ST-segment depression or T-wave inversion, left ventricular hypertrophy, angina associated with electrocardiographic changes, smoking history or presence of previous infarction. However, there was a clear association between progression to Q-wave AMI and the presence of initial S-T segment elevation ($p = 0.037$), but the predictive value of ST elevation by Q-wave development was quite low. Although ST depression was not associated with a higher rate of development of Q waves for the study group as a whole, marked horizontal ST depression with upright T waves in the "anterior" (precordial) leads V_1 to V_4 preceded the development of pathologic R-waves (posterior infarction) in >60% of these patients.

DISCUSSION

Of the 76 patients who developed pathologic Q waves after randomization, approximately 75% developed abnormal Q waves within the first 3 study days. The remaining 25% of patients developed late Q waves that were discernible only on review of the predischarge electrocardiogram (9 to 11 days after randomization). Additionally, patients who developed Q waves had significantly increased peak log CK levels. These patients also had a higher proportion of posterior infarctions than expected, probably reflecting a bias to exclude patients from randomization if they had marked ST elevation (even if Q waves were absent), but not patients with marked ST depression in the right-sided precordial leads who were judged initially to have "anterior" non-Q-wave myocardial infarction.[24] Most patients who developed Q waves after randomization had no evidence of reinfarction by enzyme determinations, but the later the Q waves developed the more likely enzymatic extension had occurred. Only 4 of the 42 patients who had Q waves by study day 2 had CK-MB–confirmed extensions, whereas 10 of the 34 patients who developed Q waves after day 3 exhibited extension.

Several reports have stressed the importance of differentiating non-Q-wave from Q-wave AMI. The former tends to exhibit smaller CK and CK-MB release, a lower incidence of totally occluded infarct-related coronary arteries despite equally severe coronary disease, higher reinfarction rates and poor long-term prognoses and pathologically is more often nontransmural in extent.[4–9,13,15,18] Few of these studies, however, deal with the electrocardiographic difficulties of differentiating the 2 infarct subtypes. Most studies have used the initial second or third 12-lead electrocardiogram (obtained only within the first 24 to 72 hours) to make the differentiation. Among the problems that have not been clearly defined are posterior infarctions in which pathologic R waves rather than Q waves develop, "electrocardiographic lag" in which the Q waves may evolve more slowly after the initial event and reinfarction (or extension) resulting in new electrocardiographic Q waves. The problem of "lag" is particularly important because all infarctions, whether Q- or non-Q-wave, presumably start without Q-waves.

Our study, which randomized a large number of patients with CK-MB–confirmed non-Q-wave AMI, addressed these problems. Randomization occurred at a mean of 50 hours after onset of chest pain, at which time Q waves were not present. Thus, the late development of Q waves or pathologic R waves could be assessed. Because plasma CK and CK-MB samples were measured every 12 hours for up to 14 days, the association between isoenzyme-defined extension and the development of Q waves could be rigorously determined. Review of all entrance electrocardiograms by 5 qualified electrocardiographers enabled the determination of the false randomization rate (i.e., that fraction of patients erroneously called non-Q-wave at entrance into study). There were 32 such misrandomizations, many of which were early albeit unrecognized posterior infarcts. The difficulty in assessing the early electrocardiographic findings during acute posterior infarction, as assessed from the Diltiazem Reinfarction Study database, has recently been reported.[24]

Clinical implications: We emphasize some of the difficulties in the electrocardiographic differentiation of Q-wave from non-Q-wave AMI. Early posterior infarctions are often misidentified as "anterior" non-Q-wave AMI, because of precordial ST-segment depression.[24] Our data indicate that Q waves often develop >72 hours after myocardial infarction; indeed, in about 25% of cases, they develop only by the predischarge tracing. As shown by our study, enzymatic reinfarction may "convert" a non-Q- to a Q-wave infarction in a minority of cases. Patients who do develop Q-wave AMI after non-Q-wave infarction have higher enzymatic levels at entry. We, however, found no demographic or electrocardiographic criteria that permitted further prediction of Q-wave development. Although ST-segment elevation was significantly associated with Q-wave development, its predictive value was quite low. T-wave inversion and ST depression did not predict development of Q-wave AMI, irrespective of the magnitude of change.

Despite the fact that patients who developed Q waves at study day 3 (i.e., day 6 after AMI) or later were more likely to have CK-MB–confirmed extension, most patients with late development of Q waves did not have extensions; thus, electrocardiographic lag rather than extension is the most common cause of late development of Q waves. We conclude that better separation of Q-wave from non-Q-wave AMI can be made by analysis of multiple electrocardiograms obtained throughout the patient's hospitalization.

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Detection of Restenosis After Elective Percutaneous Transluminal Coronary Angioplasty Using the Exercise Treadmill Test

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To determine the value of a 6-month exercise treadmill test for detecting restenosis after elective percutaneous transluminal coronary angioplasty (PTCA), 303 consecutive patients with successful PTCA and without a recent myocardial infarction were studied. Among the 228 patients without interval cardiac events, early repeat revascularization or contraindications to treadmill testing, 209 (92%) underwent follow-up angiography, and 200 also had a follow-up treadmill test and formed the study population. Restenosis (≥75% luminal diameter stenosis) occurred in 50 patients (25%). Five variables were individually associated with a higher risk of restenosis: recurrent angina ($p = 0.0002$), exercise-induced angina ($p = 0.0001$), a positive treadmill test ($p = 0.008$), more exercise ST deviation ($p = 0.04$) and a lower maximum exercise heart rate ($p = 0.05$). However, only exercise-induced angina ($p = 0.002$), recurrent angina ($p = 0.01$) and a positive treadmill test ($p = 0.04$) were independent predictors of restenosis. Using these 3 variables, patient subsets could be identified with restenosis rates ranging from 11 to 83%. The exercise treadmill test added independent information to symptom status about the risk of restenosis after elective PTCA. Nevertheless, 20% of patients with restenosis had neither recurrent angina nor exercise-induced ischemia at follow-up. For more accurate detection of restenosis, the exercise treadmill test must be supplemented by a more definitive test.

(Am J Cardiol 1990;65:28–34)

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Since the first percutaneous transluminal coronary angioplasty (PTCA) was performed in 1977,[1] it has been used as an alternative to bypass graft surgery or medical therapy for many patients with coronary artery disease.[2] Unfortunately, restenosis after an initially successful PTCA remains a significant problem, occurring in 12 to 40% of patients within the first 6 months after the procedure.[3–10] Coronary angiography has been used to detect restenosis and to aid decision making about the need for further intervention. Serial angiograms, however, are time-consuming, costly and associated with risk. Several studies have examined the value of noninvasive testing, including thallium-201 imaging[11–14] and exercise radionuclide ventriculography,[15] for detecting restenosis after successful PTCA. These tests are more expensive and less readily available than standard treadmill exercise testing. Thus, it would be helpful to know whether clinicians can rely on a standard treadmill test, in addition to clinical symptoms, to follow patients after successful PTCA. The accuracy of the test in this setting, however, remains incompletely defined. In addition, no previous evaluation of noninvasive testing for restenosis has had more than a 75% rate of follow-up angiography. This study examines the value of the exercise treadmill test for detecting restenosis in a large consecutive population of patients with successful elective PTCA and a high rate of angiographic follow-up.

METHODS

Patient population: We identified 325 consecutive patients without a recent (≤6 weeks) myocardial infarction who underwent an elective PTCA for native coronary artery disease (stenosis ≥75%) at Duke University Medical Center during a 1-year period (April 1986 to April 1987). Of these, 303 (93%) had a successful procedure and were considered potentially eligible for the Duke PTCA restenosis follow-up protocol, involving a repeat coronary angiogram and an exercise treadmill test approximately 6 months after PTCA (Figure 1). Thirty-two patients did not have follow-up angiography: 3 died (2 from cardiovascular causes and 1 by suicide), 9 had medical contraindications to repeat angiography (cerebrovascular disease in 4, renal failure in 3, severe congestive heart failure in 1 and anticoagulation in 1), 13 refused the test (or the referring physician refused), 4 lived out of state and 3 could not be contacted. Thus, 271 eligible patients (89%) had a repeat angiogram. In

32 patients, interim clinical events obviated the relevance of detecting restenosis by exercise testing: 5 patients had interval myocardial infarctions and 27 underwent repeat revascularization procedures (18 PTCA, 9 coronary artery bypass surgery) after returning with recurrent symptoms before scheduled follow-up. Thirty additional patients were deemed ineligible for exercise testing because of unstable angina at the time of follow-up. Among the 209 remaining eligible patients, 200 (96%) had both follow-up catheterization and an exercise treadmill test and formed the final study population.

Data collection and information system: The computerized medical information system used in this study has been described in detail.[16–18] Before both PTCA and follow-up catheterization, each patient had a cardiac history, physical examination and a resting 12-lead electrocardiogram. Baseline risk factors for coronary artery disease were defined as described previously[19]: hypertension was a current systolic blood pressure >140 mm Hg or a history of hypertension; hyperlipidemia was the presence of a fasting serum cholesterol level ≥250 mg/dl or a history of hyperlipidemia; a family history was considered present if first-degree relatives had coronary artery disease before age 60. Symptoms at the time of follow-up were classified as follows: (1) asymptomatic or nonanginal discomfort, defined as discomfort that clearly has a noncardiac etiology; (2) atypical angina, defined as discomfort that could not be clearly classified as either typical or nonanginal; and (3) typical angina, defined as discomfort reproducibly precipitated by increased cardiac workload, located appropriately, visceral in quality and relieved promptly after removal of the precipitating factors or after use of nitroglycerin.[20] Angina severity was assessed according to the Canadian Cardiovascular Society criteria.[21]

Angioplasty and follow-up coronary angiography: PTCA was performed using an 8Fr thin wall guiding catheter and a low-profile balloon catheter. Successful PTCA was defined as a reduction in coronary luminal diameter stenosis immediately after PTCA to ≤50% of luminal diameter, as determined visually by consensus of ≥2 experienced angiographers. Patients were routinely given heparin intravenously at the start of the PTCA procedure, and received aspirin (325 mg/day), dipyridamole (75 mg 3 times a day) and a calcium antagonist from the time of PTCA until follow-up.[5]

Follow-up coronary angiography was performed on an outpatient basis using the Judkins technique with 5Fr or 6Fr catheters. The luminal diameter stenosis at the site of the previously successful PTCA was graded on an ordinal scale (0, <25, 25, 50, 75, 95 or 100%) for each patient by at least 2 angiographers, as described and validated previously.[17,22] Angiographic restenosis was defined as the presence of a ≥75% luminal diameter narrowing at the PTCA site.[3,5] When angioplasty was performed on >1 artery (n = 20), restenosis was defined as recurrence of a ≥75% luminal narrowing in ≥1 of the vessels.

Treadmill testing: Standard Bruce protocol exercise treadmill tests[23,24] were performed on the same day as the catheterization in all but 6 cases, and within 2 days in all patients. Patients receiving β-adrenergic blocking drugs were instructed to taper the doses so that no such drugs were being taken 2 days before testing. Exercise was continued until the target heart rate was achieved, or until the development of limiting symptoms (angina, dyspnea, fatigue or claudication), abnormalities of rhythm (ventricular tachycardia or frequent couplets) or marked and progressive ST-segment displacement (≥0.20 mV in the presence of typical angina or in the first stage of exercise).

All test results were reviewed by one of the investigators independently of the clinical data and blinded to the outcome assessment. Any ST-segment deviation ≥0.10 mV relative to the baseline that occurred during or after exercise in 3 consecutive beats and that was horizontal or sloping away from the baseline at 0.08 second after the J point was measured to the nearest 0.05 mV using a calibrated grid. Each test was classified according to standardized criteria[24] into one of the following interpretations: (1) positive, if the ST segment was horizontal or downsloping and was depressed ≥0.10 mV from the resting electrocardiographic baseline at 0.08 second after the J point, or the ST segment was elevated ≥0.10 mV from the resting baseline in leads

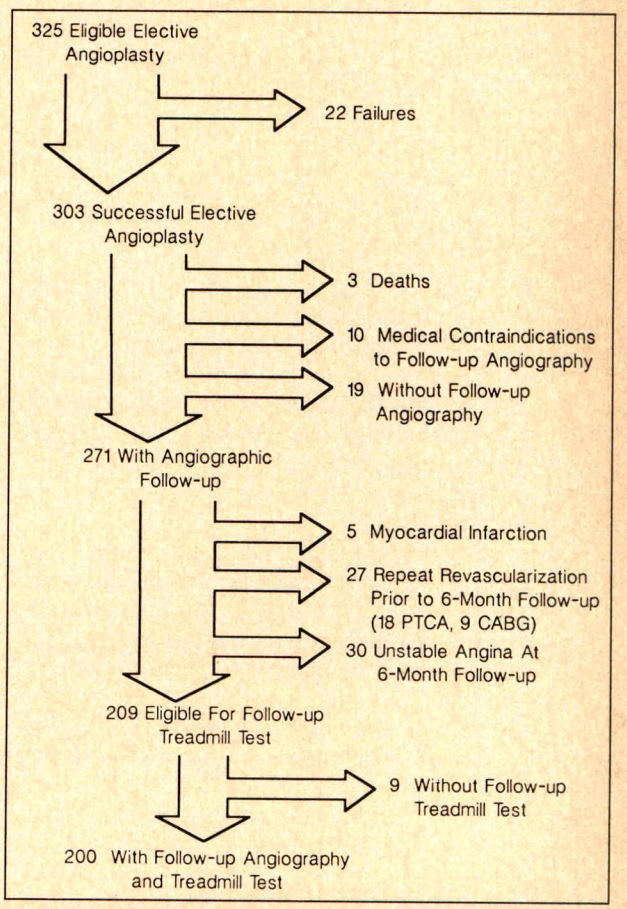


FIGURE 1. Derivation of final study population from 325 consecutive elective coronary angioplasty procedures at Duke over a 1-year period. CABG = coronary artery bypass graft surgery; PTCA = percutaneous transluminal coronary angioplasty.

TABLE I Baseline Clinical Characteristics*

	Restenosis (n = 50)	%	Other Significant Disease (n = 46)	%	No Significant Disease (n = 104)	%
Male sex	37	74	33	72	68	65
Hypertension	28	56	23	50	45	43
Diabetes mellitus	9	18	8	17	15	14
Family history of premature heart disease	31	62	35	76	61	59
Smoking history	29	58	32	70	57	55
Hyperlipidemia	19	38	19	41	51	49
History of myocardial infarction	14	28	21	46	20	19
Age (yrs)*	59	53–66	56	49–65	59	50–65

* Data shown are medians (25th to 75th percentile).

TABLE II Baseline Angiographic Characteristics

	Restenosis (n = 50)	%	Other Significant Disease (n = 46)	%	No Significant Disease (n = 104)	%
Angioplasty artery						
LAD	26	52	21	46	44	42
LAD/LCX	3	6	1	2	4	4
LCX	8	16	11	24	15	14
LCX/RCA	2	4	1	2	6	6
RCA	10	20	11	24	34	33
LAD/RCA	1	2	1	2	1	1
Number of diseased vessels						
1	32	64	17	37	85	82
2	13	26	19	41	19	18
3	5	10	10	22	0	0
Ejection fraction*	56	49–60	54	47–60	59	53–64

* Data shown are medians (25th to 75th percentile).
LAD = left anterior descending; LCX = left circumflex; RCA = right coronary artery.

without Q waves; (2) negative adequate, if the patient reached 85% of the maximal predicted heart rate without significant ST-segment changes; (3) negative inadequate or indeterminate, if there were no significant ST-segment changes, but the patient failed to reach the predicted target heart rate, or if ST elevation occurred only in leads with pathologic Q waves; and (4) uninterpretable, in the presence of left bundle branch block or an artificially paced rhythm.

A previously derived treadmill angina index[24] was used to describe exercise-induced symptoms; this index was assigned a value of 0 if angina was absent during exercise, 1 if angina occurred during exercise and 2 if angina was the reason the patient stopped exercising.

Data analysis: Continuous variables were summarized with medians and quartile ranges (25th to 75th percentile). Patient groups were compared with respect to continuous variables using Kruskal-Wallis nonparametric analysis of variance, and discrete variables using chi-square analysis. Univariate and multivariate relations between restenosis and 5 predictor variables defined before the analysis were examined using a logistic regression model.[25,26] In a second analysis, the same variables were incorporated into an ordinal logistic regression model to assess the predictive value in estimating the number of major coronary arteries (0, 1, 2 or 3) with significant stenoses at follow-up cardiac catheterization. Comparison of the results of these 2 analyses provided an assessment of the effect of significant lesions in other coronary vessels on the associations being examined. The predictor variables examined were: recurrent anginal symptoms (either typical or atypical) coded as a binary variable; the treadmill angina index; treadmill interpretation coded as 2 if positive, 1 if negative inadequate or indeterminate (uninterpretable tests were deleted from analysis) and 0 if negative adequate; the magnitude of exercise-induced ST deviation; and exercise duration in seconds. In an exploratory fashion, the relation to restenosis of 2 additional variables, maximum heart rate achieved on the treadmill and exercise systolic blood pressure, was also examined.

RESULTS

Restenosis of the PTCA lesion occurred in 98 (36%) of the 271 patients who had a successful elective PTCA and had angiographic follow-up (with or without a treadmill test). Of the 200 patients who had both follow-up angiography and a treadmill exercise test, 50 (25%) had restenosis of the PTCA lesion, 46 (23%) had no restenosis but had significant coronary disease present at other sites and 104 (52%) had no significant coronary stenoses. These 3 groups did not differ appreciably

TABLE III Treadmill Test Results

	Restenosis (n = 50)	%	Other Significant Disease (n = 46)	%	No Significant Disease (n = 104)	%
Angina during test						
None	30	60	37	80	94	90
Nonlimiting angina	10	20	5	11	7	7
Test stopped due to angina	10	20	4	9	3	3
Test interpretation						
Negative	15	30	22	48	59	57
Negative inadequate or indeterminate	16	32	9	20	24	23
positive	17	34	14	30	17	16
uninterpretable	2	4	1	2	4	4
ST-segment deviation (mV)*						
0	31	65	31	69	83	83
0.10–0.19	15	31	10	22	13	13
0.20–0.30	2	4	4	9	4	4
Maximum heart rate†	136	112–149	142	123–155	140	123–153
Peak systolic blood pressure†	170	158–200	184	155–200	177	160–191
Exercise duration (min)†	6.2	4.4–8.6	7.1	5.2–8.8	7.2	4.9–9.6

* Uninterpretable tests deleted (n = 7); † data shown are medians (25th to 75th percentile).

in age, gender or prevalence of hypertension, diabetes, family history of premature heart disease, smoking history or hyperlipidemia (Table I). More patients in the group without restenosis but with other significant stenoses had a history of myocardial infarction compared with the other 2 groups. Slightly more patients with restenosis had left anterior descending lesions, compared with the other 2 groups ($p = 0.32$) (Table II). The proportion of patients with multivessel disease on the baseline angiogram was highest in the group without restenosis but with other significant stenoses (63%), intermediate in the group with restenosis (36%) and lowest in those without stenoses (18%) ($p < 0.001$). Angioplasty was performed in >1 vessel in 20 patients; the restenosis rate was slightly higher in this group (30%) than in those having 1-vessel angioplasty (24%), but this difference was not significant ($p = 0.62$). The median ejection fraction was higher in the group without significant disease on the follow-up study ($p = 0.007$).

Figure 2 shows the distribution of anginal symptoms at the time of follow-up. Among 29 patients reporting typical anginal symptoms at follow-up, 19 (66%) had restenosis, compared with 11 of 42 (26%) with atypical symptoms, and 20 of 129 (16%) without symptoms at follow-up ($p < 0.001$). Twenty-two patients (76%) with typical symptoms had either restenosis or other significant disease, compared with 20 (48%) of those with atypical symptoms, and 54 (42%) of those with no symptoms. Among those with Canadian Cardiovascular Society class I symptoms, 25% had restenosis, compared with 38, 67 and 53% in those with class II, III and IV symptoms, respectively.

The prevalence of exercise-induced angina was highest in the restenosis group (40%), intermediate in the group with other significant lesions (20%) and lowest in the patients without significant residual disease (10%) ($p = 0.001$) (Table III). Similarly, the frequency of exercise-induced ST-segment deviation ≥0.10 mV was highest in patients with restenosis (35%) and patients with other significant disease (31%) and lower in patients without significant stenoses (17%, $p = 0.03$). The majority of patients in all 3 groups, however, had a negative or indeterminate test result. The groups did not differ appreciably in the distribution of maximum exercise heart rate or peak exercise systolic blood pressure. There was a trend toward shorter exercise duration in patients with restenosis compared with patients in the other 2 groups ($p = 0.08$).

In a stepwise logistic regression analysis (Table IV), exercise-induced angina was the strongest individual predictor of restenosis ($p = 0.0001$). After adjusting for the association between exercise angina and restenosis,

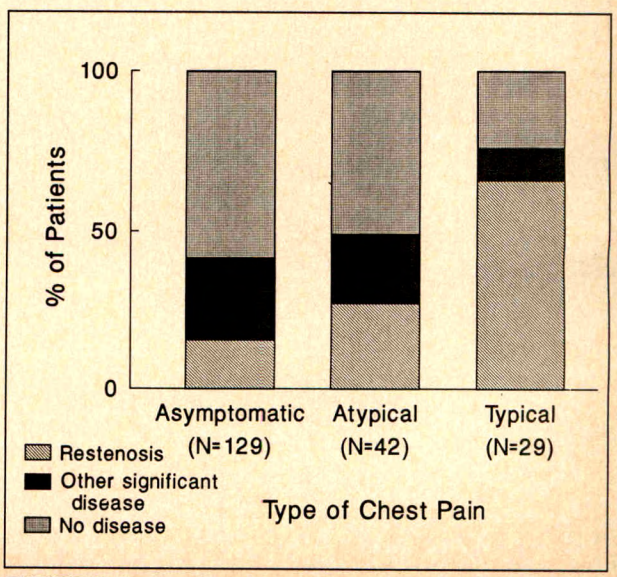


FIGURE 2. Status of anginal symptoms at the time of follow-up testing in the 200 study patients.

TABLE IV Logistic Regression Model for Restenosis After PTCA

Variable	Univariable Chi-square	p Value	Multivariable Chi-square	p Value
Angina during ETT	18	0.0001	18	0.0001
Angina at follow-up	14	0.0002	6	0.01
ETT interpretation	7	0.009	4	0.05
Maximum ST-segment deviation	3	0.08	—	
Maximum heart rate	3	0.08	—	
Exercise duration	3	0.07	—	

Variables are listed in order of entrance into stepwise logistic regression model. Multivariable chi-square for each variable is adjusted for all preceding variables.
ETT = exercise treadmill test; PTCA = percutaneous transluminal coronary angioplasty.

recurrent angina (p = 0.01) continued to have a significant association with restenosis, followed by test interpretation (p = 0.05). When the regression analysis was repeated using the number of diseased vessels present at the follow-up catheterization study as the dependent variable, exercise-induced angina again had the strongest association (p = 0.0001), followed by the magnitude of exercise-induced ST-segment deviation (p = 0.003) and exercise duration (p = 0.03).

Finally, the study population was stratified by recurrent angina, exercise-induced angina and treadmill test interpretation (Figure 3). The likelihood of restenosis was directly related to the presence of these 3 characteristics and was present in 83% of patients with all 3, 36 to 56% of patients with any 2 and 21 to 29% of patients with only 1 characteristic. Ten of 89 patients (11%) without any of the 3 characteristics had restenosis. The sensitivity of either exercise-induced angina or significant exercise-induced ST-segment changes for restenosis, after eliminating patients with uninterpretable tests, was 60%, whereas the specificity was 69%. The positive and negative predictive values of the test were 61 and 84%, respectively. In patients with recurrent angina, the positive predictive value of the treadmill test for restenosis was 53%; the negative predictive value was 71%. The corresponding values in patients without recurrent angina were 26 and 89%. Because a positive test could be due to stenosis at the angioplasty site or in another vessel, we examined the effect of eliminating patients with significant stenoses in other vessels as a result of incomplete revascularization or increase in a previously insignificant stenosis. The sensitivity of the test was not

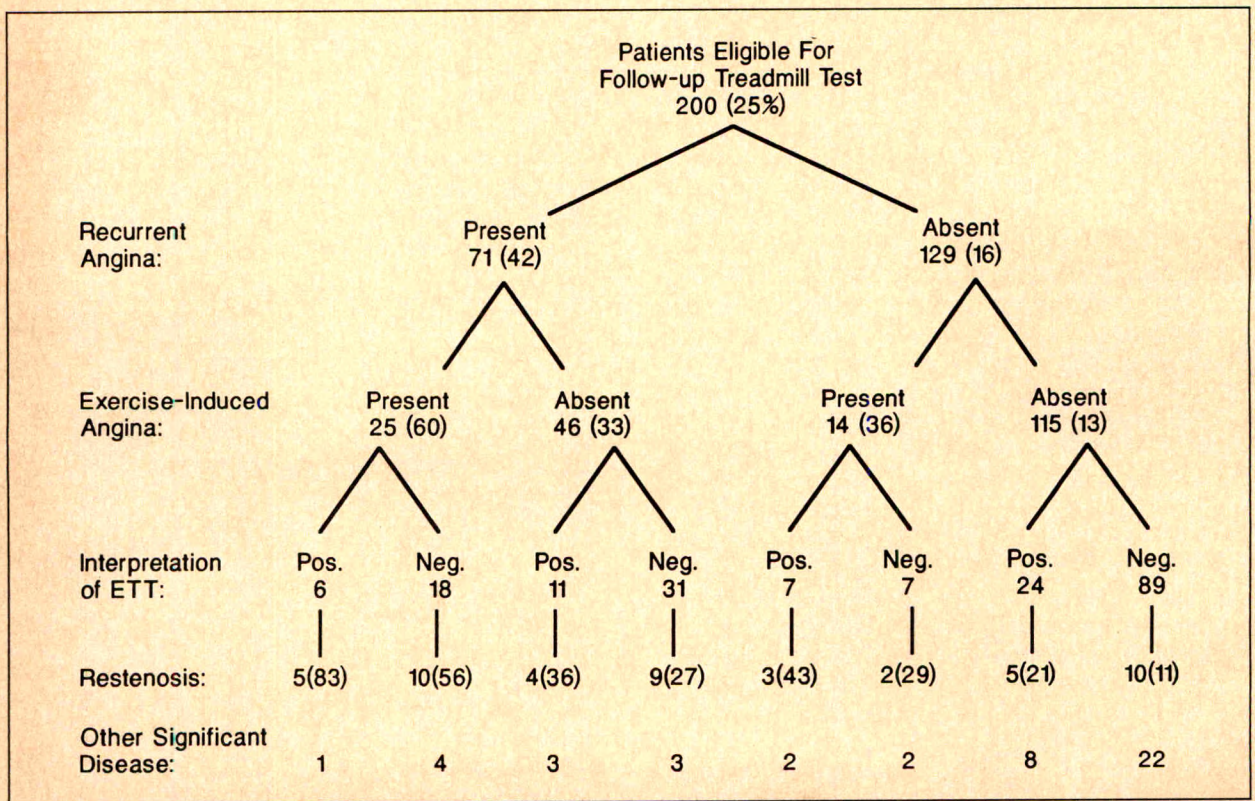


FIGURE 3. Stratification of study population by presence or absence of symptoms at follow-up, exercise-induced angina and treadmill test interpretation. Number of patients in each stratum is shown, along with corresponding restenosis rate in parentheses. Patients with uninterpretable tests (n = 7) are omitted from the lowest stratum. Below each group the number with restenosis is shown. ETT = exercise treadmill test.

changed by such subgrouping, and the specificity increased only slightly, to 75%. We also examined how the sensitivity and specificity of the treadmill test result varied according to which vessel was dilated. For left anterior descending lesions, the sensitivity was 59% and the specificity was 75%. The corresponding figures for circumflex and right coronary lesions were 62 and 72%, and 67 and 58%, respectively.

DISCUSSION

Our study shows that in patients able to perform a follow-up treadmill test 6 months after elective PTCA, the presence of exercise-induced ischemia improves the clinician's ability to detect restenosis, beyond the contribution of the patient's symptom status. The overall accuracy of the test, however, is only fair, as would be expected in a population with predominantly 1-vessel disease,[27] and the test is negative in a substantial minority of patients with angiographic restenosis. A unique feature of this study is that 6-month follow-up exercise tests and repeat coronary angiograms were obtained in 88% of patients eligible for both studies after a successful PTCA, a much higher rate than any previous study of noninvasive testing to detect restenosis.

Long-term restenosis rate: The restenosis rate in this group of patients undergoing elective PTCA is comparable to that found in other studies.[3,5,28] The variability in rates reported in these studies can be explained in part by differences in the definition of restenosis,[28] and perhaps by variability in completeness of angiographic follow-up. In addition, the restenosis rate in a subset of patients who were able to undergo exercise treadmill testing was lower than the rate in patients who were not tested, because most of the latter group underwent evaluation before their scheduled follow-up date because of unstable angina.

Relation of treadmill test result to restenosis: Our results are similar to those of previous studies that examined the ability of exercise testing to detect restenosis. Wijns et al,[14] for example, found in a group of 89 patients that the positive predictive value of either horizontal ST-segment depression or angina occurring during the treadmill test was 50%, whereas the negative predictive value was 65%. Ernst et al[11] studied 25 patients who underwent treadmill testing 4 to 8 months after PTCA, and found a sensitivity of 75%, a specificity of 85% and a positive predictive value of 50%.

The substantial number of false negative results in this study is at least partially due to the large proportion of patients with 1-vessel disease, in whom the sensitivity of treadmill testing is known to be lower.[27] Conversely, nearly half of the patients who had positive treadmill tests but were not found to have angiographic restenosis ("false positive" treadmill tests) had other significant stenoses at the time of follow-up, which could have caused an ischemic response to exercise. Furthermore, the functional significance of a stenosis <75% in the PTCA vessel may also have been underestimated. As Rosing et al[29] speculated, the use of diameter narrowing <75% to define absence of restenosis may have misclassified some patients with long lesions or significant reductions in absolute vessel diameter, who consequently had ischemia during treadmill testing.

The usefulness of an exercise treadmill test for managing a patient after PTCA can be maximized by considering each of the components of the test, rather than simply examining the overall test interpretation. In this study, we hypothesized that the test interpretation, duration of exercise, maximum ST-segment deviation from baseline and presence of angina during the test would be most strongly related to the presence of restenosis. The relatively small number of patients who were found to have restenosis limited the number of predictor variables that could reasonably be analyzed with the logistic regression model. The occurrence of angina during the treadmill test was more strongly related to the presence of restenosis than were angina reported at the time of follow-up or any of the other treadmill variables. Despite the statistical strength of this association and the additional information yielded by the presence of angina at follow-up or a positive treadmill test, 10 of the 50 patients (20%) with angiographic restenosis were still missed by requiring ≥1 of these criteria to be present.

Limitations: Several limitations of our study should be noted. First, the association between any variable and restenosis is greatly influenced by the definition of restenosis. The use of a standard dichotomous definition (present vs absent) for restenosis may have diluted some associations present in the data. Second, the ability to demonstrate an association between any set of independent variables and restenosis is limited by the number of patients with restenosis. Our study population was large enough, however, to detect several strong predictors of restenosis. Finally, the relative prognostic importance of detected and undetected restenosis in this population could not be determined because most patients with restenosis were referred for repeat revascularization procedures.

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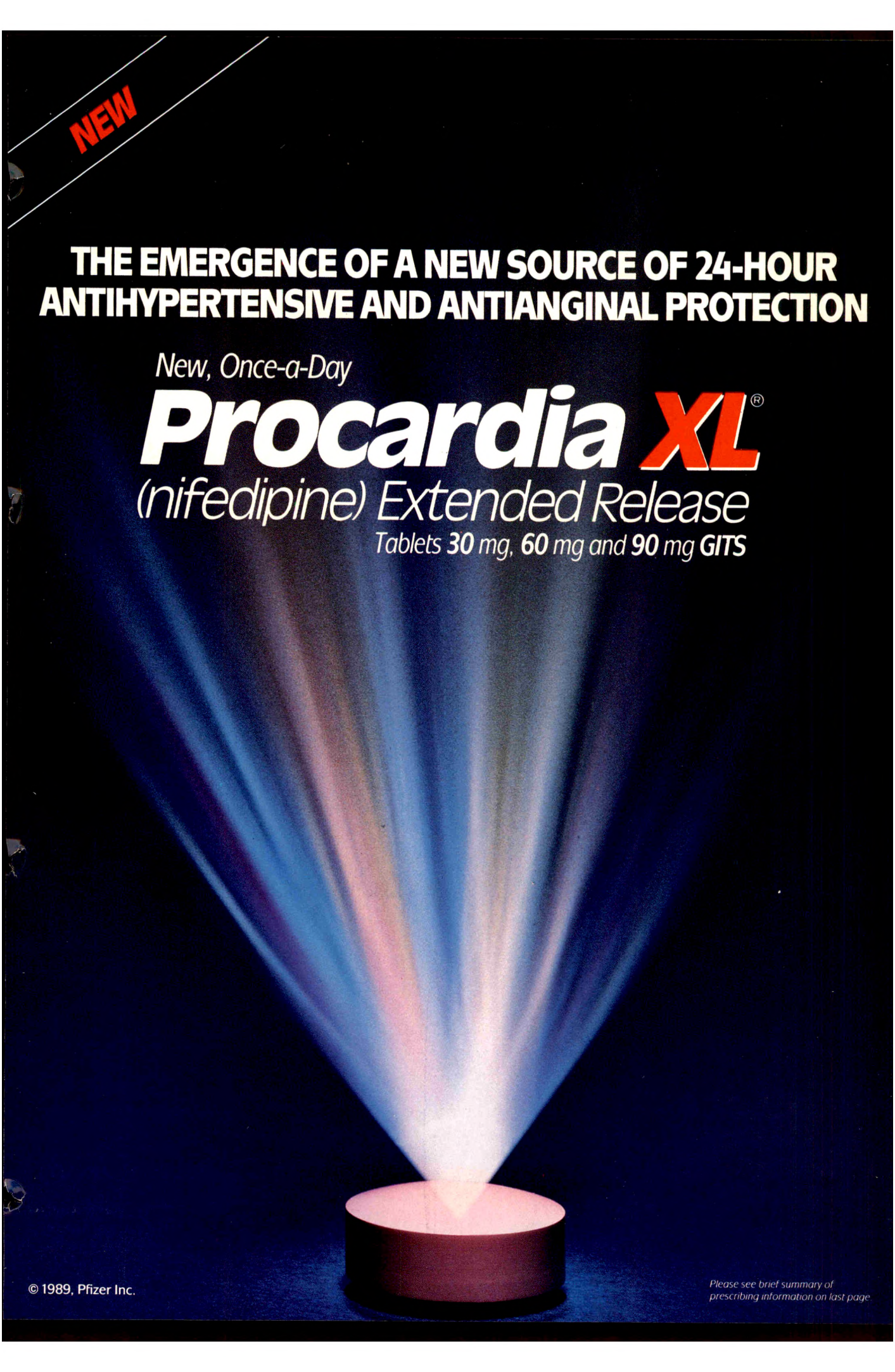
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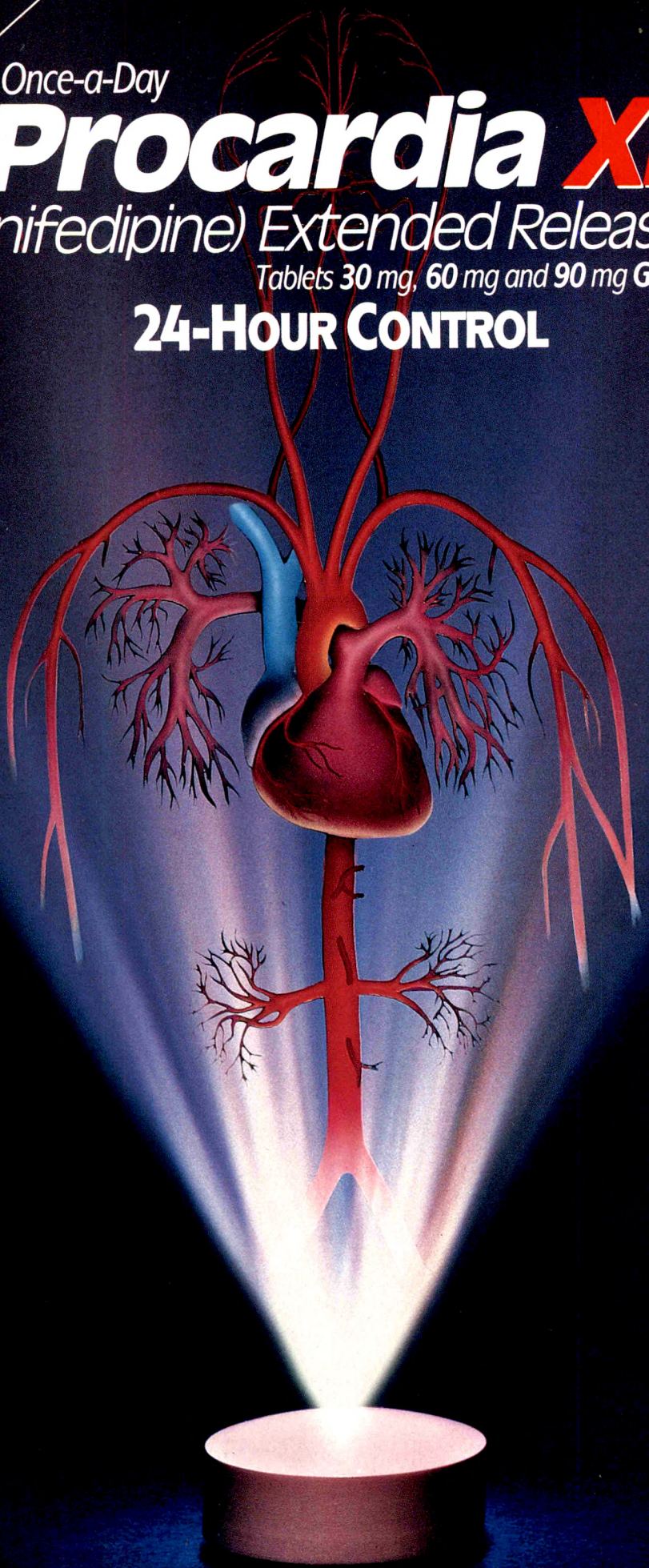
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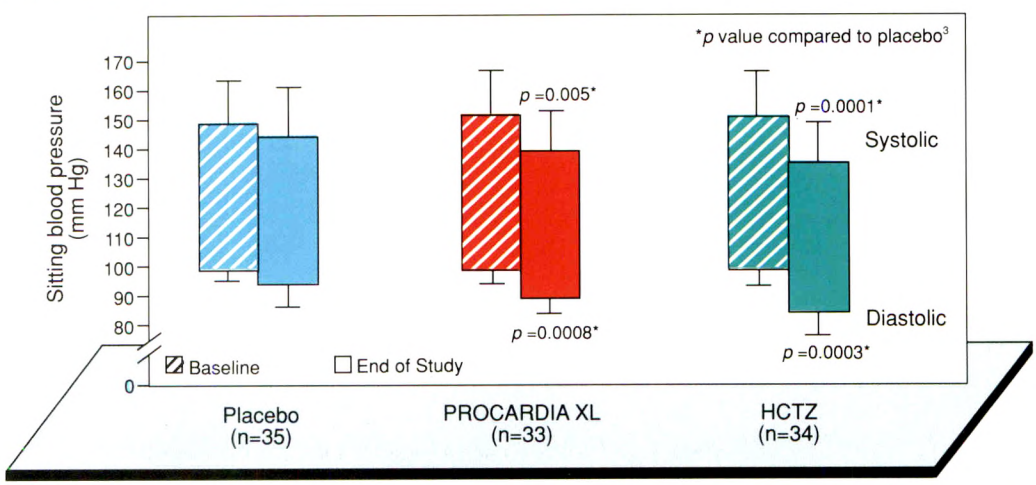
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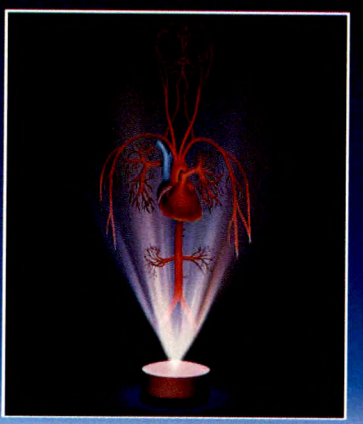
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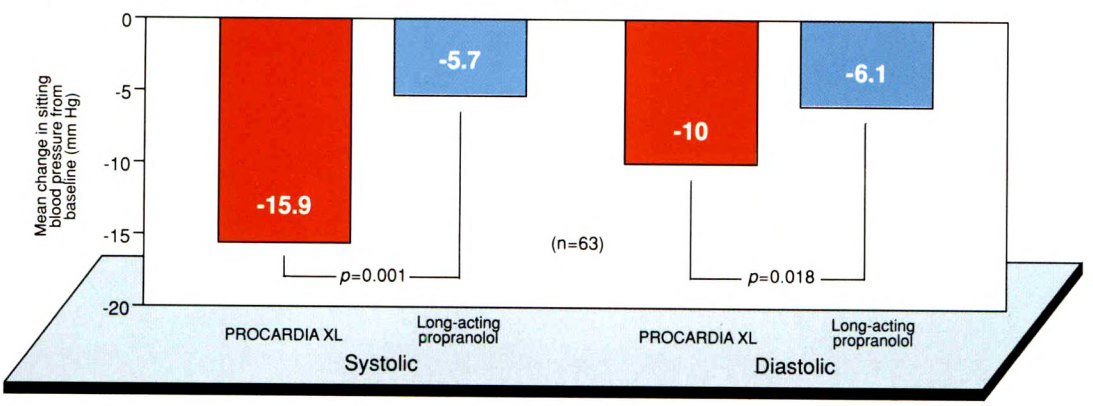


Double-blind, 14-week, parallel study comparing PROCARDIA XL (30-60 mg *q.d.*) with hydrochlorothiazide (25-50 mg *q.d.*) and placebo in 102 patients of different races with mild to moderate hypertension. BP measurements were made 24 hours after last dose. Goal BP was defined as diastolic BP $\leq$90 mm Hg. (Reported by Gavras I et al, *Am J Med*, 1987.[1])



Results of a Double-Blind, 14-Week, Parallel Study of PROCARDIA XL and Long-Acting Propranolol in 63 Hypertensive Patients[2]:

DECREASE IN SITTING BLOOD PRESSURE FROM BASELINE[2]



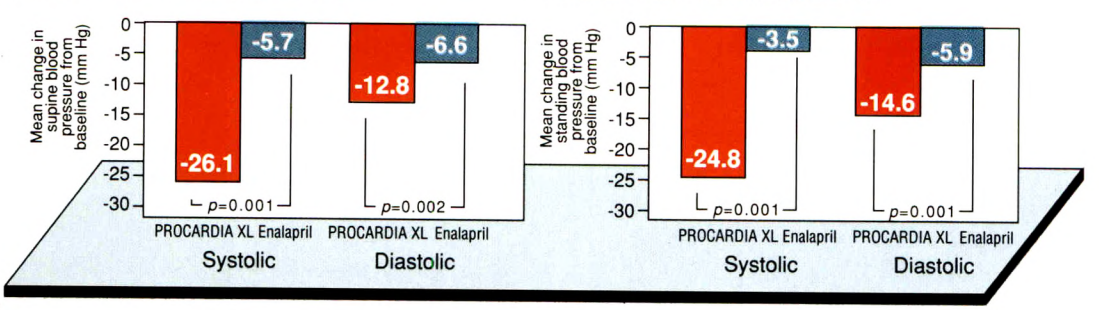
Double-blind, 14-week, parallel study to compare the efficacy and safety of PROCARDIA XL (30-90 mg *q.d.*) and long-acting propranolol (80-240 mg/day) in 63 patients of different races with moderate essential hypertension (sitting diastolic BP 95-110 mm Hg) who were already receiving diuretics. BP measurements were made at 24 hours after last dose. (Reported by Frishman WH et al, *Am J Cardiol*, 1989.[2])

Baseline sitting BP: PROCARDIA XL — 150/102 mm Hg; long-acting propranolol — 143/101 mm Hg. (Data on file. Medical Department, Pfizer Laboratories, Pfizer Inc.[4])

Results of a Single-Blind, Randomized Trial of PROCARDIA XL and Enalapril in Black Hypertensive Patients[4]:

DECREASE IN SUPINE BLOOD PRESSURE FROM BASELINE[4]

DECREASE IN STANDING BLOOD PRESSURE FROM BASELINE[4]



Single-blind, randomized trial to compare PROCARDIA XL (30-150 mg *q.d.*) with enalapril (5-40 mg *q.d.*) in 67 black hypertensive patients. At end of titration, data were evaluable in 64 patients. Mean baseline supine BP: PROCARDIA XL — 165/102 mm Hg; enalapril — 160/100 mm Hg. Mean baseline standing BP: PROCARDIA XL — 162/105 mm Hg; enalapril — 156/104 mm Hg. BP was measured 24 hours after the last dose on final titration visit. (Data on file. Medical Department, Pfizer Laboratories, Pfizer Inc.[4])

Please see brief summary of prescribing information on last page.

NEW, ONCE-A-DAY FOR ANGINA

Procardia XL®

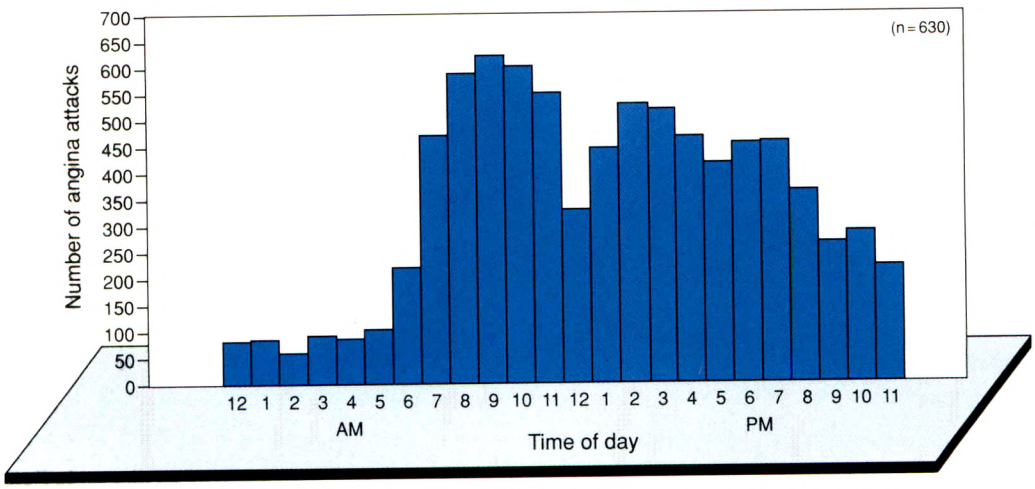
(nifedipine) Extended Release

Tablets **30** mg, **60** mg and **90** mg **GITS**

Angina Attacks Peak in the Early Morning

- There is a significant circadian variation in the pattern of occurrence of angina attacks, as recorded in patient diaries, with peak angina activity occurring in the early morning[4]

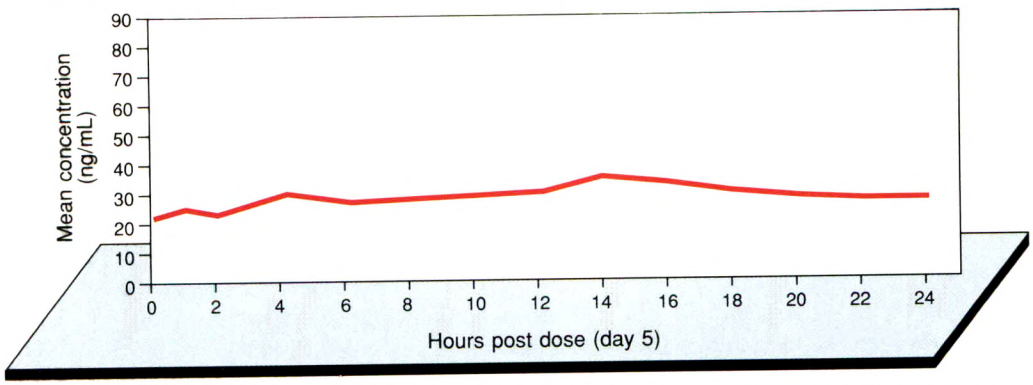
CIRCADIAN PATTERN OF ANGINA ATTACKS[4]



Data from multiple controlled trials in 630 patients with chronic stable angina treated only with sublingual nitroglycerin.[4]

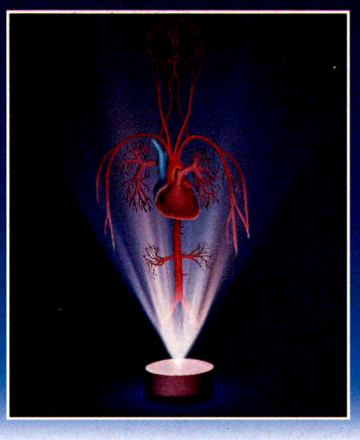
Now, Once-Daily Dosing Delivers Essentially Constant 24-Hour Plasma Levels

MEAN STEADY-STATE PLASMA CONCENTRATIONS WITH PROCARDIA XL TABLETS[4]



Mean steady-state plasma concentrations of PROCARDIA XL 60 mg *q.d.* in 21 healthy volunteers. (Data on file. Medical Department, Pfizer Laboratories, Pfizer Inc.[4])

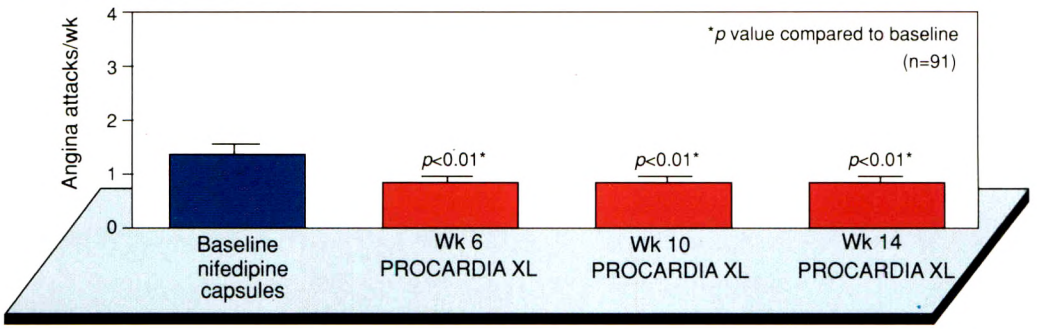
Please see brief summary of prescribing information on last page.



ONCE-DAILY DOSING CONTROLS ANGINA FOR A FULL 24 HOURS

The Effectiveness You Expect From Nifedipine

ANGINA FREQUENCY[3]

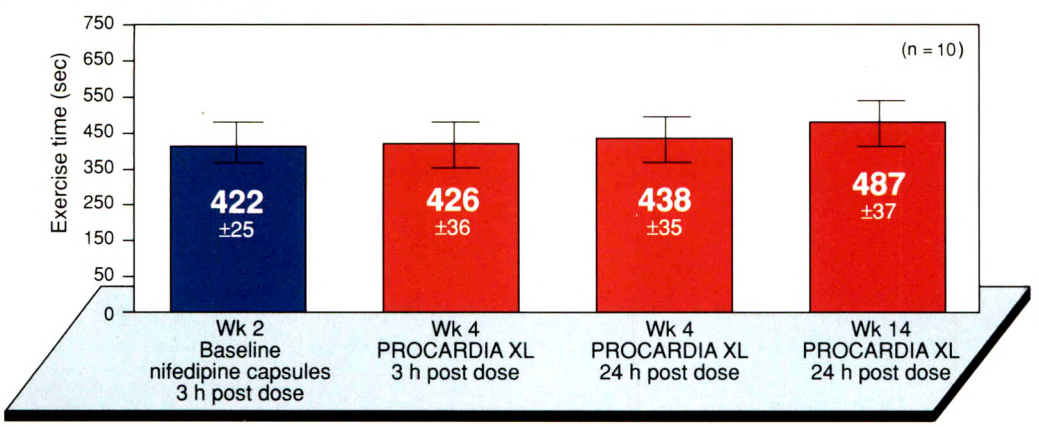


Fourteen-week, open-label, crossover trial to compare the efficacy and dose equivalency of nifedipine capsules (weeks 1 and 2) vs PROCARDIA XL (weeks 3-14) in 98 patients with chronic stable angina who had been on nifedipine capsules at least one month prior to the study. Ninety-five patients were crossed over to receive PROCARDIA XL at the nearest equivalent daily dose (over the dose range of 30-150 mg/day); 91 of these were evaluated for efficacy. The majority remained on beta blockers and/or nitrates throughout the study. (Reported by Vetrovec GW et al, *Am J Med*, 1987.[3])

Patients were of different races. (Data on file. Medical Department, Pfizer Laboratories, Pfizer Inc.[4])

No Development of Tolerance[3,7]

MEAN EXERCISE TIME[7]



Open-label, 14-week, crossover trial to compare the efficacy and dose equivalency of nifedipine capsules (weeks 1 and 2) versus PROCARDIA XL (weeks 3-14) in 10 patients with stable angina. Total daily nifedipine doses were: nifedipine capsules: 30-60 mg/day (mean = 40 mg/day); PROCARDIA XL: 30-60 mg *q.d.* (mean = 39 mg *q.d.*). Patients remained on other antianginal medication throughout the study, including beta blockers and/or nitrates. Serial treadmill exercise testing was performed at baseline while on nifedipine capsules, at 2 weeks of treatment with PROCARDIA XL and after 12 weeks of treatment with PROCARDIA XL. (Reported by Vetrovec GW et al, *Am Heart J*, 1988.[7])

Patients were of different races. (Data on file. Medical Department, Pfizer Laboratories, Pfizer Inc.[4])

- No tolerance was reported after 12 weeks of PROCARDIA XL therapy[7]

New, Once-a-Day

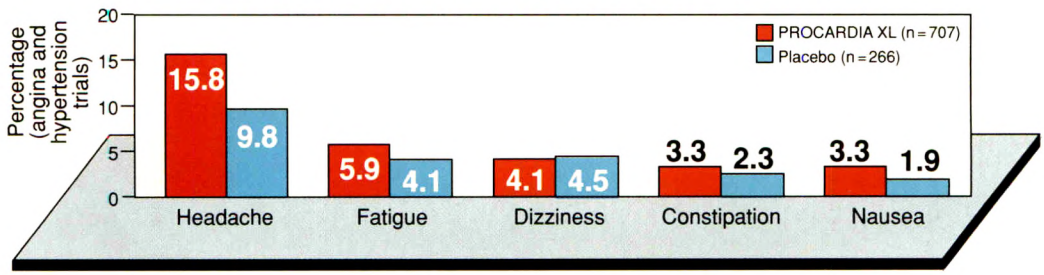
Procardia XL®

(nifedipine) Extended Release

Tablets **30** mg, **60** mg and **90** mg **GITS**

A Low Incidence of Side Effects[4]

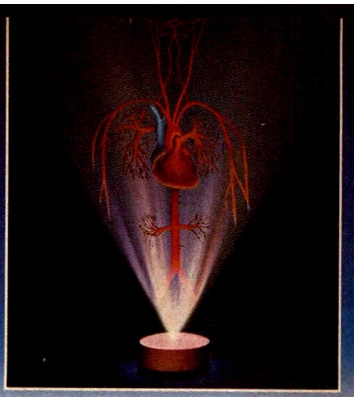
% INCIDENCE OF ADVERSE EXPERIENCES COMPARED TO PLACEBO



- Only edema and headache were more common in PROCARDIA XL patients than in placebo patients
- Edema occurs in a dose-dependent manner, with an incidence range of approximately 10% to 30% at the highest dose studied (180 mg)
- Edema is not associated with fluid retention, as evidenced by no mean weight gain in a multicenter study of 164 patients treated with PROCARDIA XL for 13-18 weeks[8]
- In controlled trials of 776 patients with PROCARDIA XL, edema resulted in discontinuation of therapy in 2.7% of patients[4]

Please see brief summary of prescribing information on last page.

24-HOUR CONTROL FOR BOTH HYPERTENSION AND ANGINA WITH ONCE-DAILY DOSING



EASY TO INITIATE ONCE-DAILY DOSING

- Initiate once-a-day therapy with a single 30-mg or 60-mg PROCARDIA XL Extended Release Tablet, swallowed whole

EASY TO SWITCH TO ONCE-DAILY DOSING

- Over 90% of angina patients controlled on nifedipine capsules were easily switched to and controlled on PROCARDIA XL Extended Release Tablets at the nearest equivalent total daily dose; others needed dosage adjustment[4]

TITRATION SHOULD PROCEED AS CLINICALLY WARRANTED

- For full dosage instructions, see prescribing information

References: **1.** Gavras I, Mulinari R, Gavras H, et al: Antihypertensive effectiveness of the nifedipine gastrointestinal therapeutic system. *Am J Med* 1987;83(suppl 6B):20-23. **2.** Frishman WH, Garofalo JL, Rothschild A: The nifedipine gastrointestinal therapeutic system in the treatment of hypertension. *Am J Cardiol* 1989;64(suppl to No. 11):65F-69F. **3.** Vetrovec GW, Parker VE, Cole S, et al: Nifedipine gastrointestinal therapeutic system in stable angina pectoris: Results of a multicenter open-label crossover comparison with standard nifedipine. *Am J Med* 1987;83(suppl 6B): 24-29. **4.** Data on file. Medical Department, Pfizer Laboratories, Pfizer Inc, New York. **5.** Chung M, Reitberg DP, Gaffney M, et al: Clinical pharmacokinetics of nifedipine gastrointestinal therapeutic system: A controlled-release formulation of nifedipine. *Am J Med* 1987;83(suppl 6B):10-14. **6.** Swanson DR, Barclay BL, Wong PSL, et al: Nifedipine gastrointestinal therapeutic system. *Am J Med* 1987;83(suppl 6B):3-9. **7.** Vetrovec GW, Parker VE, Alpert DA: Comparative dosing and efficacy of continuous-release nifedipine versus standard nifedipine for angina pectoris: Clinical response, exercise performance, and plasma nifedipine levels. *Am Heart J* 1988;115(4):793-798. **8.** Krakoff LR, Bravo EL, Tuck MK, et al: Antihypertensive and metabolic effects of nifedipine gastrointestinal therapeutic system (NGITS) in essential hypertension, abstracted. American Society of Hypertension, 4th Scientific Meeting, New York, May 10-12, 1989.

Brief Summary
PROCARDIA XL® (nifedipine) Extended Release Tablets For Oral Use
CONTRAINDICATIONS: Known hypersensitivity reaction to nifedipine.
WARNINGS: Excessive Hypotension: Although in most angina patients the hypotensive effect of nifedipine is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving nifedipine together with a beta-blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of nifedipine and a beta blocker, but the possibility that it may occur with nifedipine alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In nifedipine-treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for nifedipine to be washed out of the body prior to surgery.

The following information should be taken into account in those patients who are being treated for hypertension as well as angina:
Increased Angina and/or Myocardial Infarction: Rarely, patients, particularly those who have severe obstructive coronary artery disease, have developed well documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting nifedipine or at the time of dosage increase. The mechanism of this effect is not established.
Beta Blocker Withdrawal: It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning nifedipine. Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of nifedipine treatment will not prevent this occurrence and on occasion has been reported to increase it.
Congestive Heart Failure: Rarely, patients usually receiving a beta blocker, have developed heart failure after beginning nifedipine. Patients with tight aortic stenosis may be at greater risk for such an event, as the unloading effect of nifedipine would be expected to be of less benefit to those patients, owing to their fixed impedance to flow across the aortic valve.
PRECAUTIONS: General—Hypotension: Because nifedipine decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of nifedipine is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See WARNINGS.)
Peripheral Edema: Mild to moderate peripheral edema occurs in a dose dependent manner with an incidence ranging from approximately 10% to about 30% at the highest dose studied (180 mg). It is a localized phenomenon thought to be associated with vasodilation of dependent arterioles and small blood vessels and not due to left ventricular dysfunction or generalized fluid retention. With patients whose angina or hypertension is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.
Laboratory Tests: Rare, usually transient, but occasionally significant elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted. The relationship to nifedipine therapy is uncertain in most cases, but probable in some. These laboratory abnormalities have rarely been associated with clinical symptoms; however, cholestasis with or without jaundice has been reported. A small (5.4%) increase in mean alkaline phosphatase was noted in patients treated with PROCARDIA XL. This was an isolated finding not associated with clinical symptoms and it rarely resulted in values which fell outside the normal range. Rare instances of allergic hepatitis have been reported. In controlled studies, PROCARDIA XL did not adversely affect serum uric acid, glucose, or cholesterol. Serum potassium was unchanged in patients receiving PROCARDIA XL in the absence of concomitant diuretic therapy, and slightly decreased in patients receiving concomitant diuretics.

Nifedipine, like other calcium channel blockers, decreases platelet aggregation *in vitro*. Limited clinical studies have demonstrated a moderate but statistically significant decrease in platelet aggregation and increase in bleeding time in some nifedipine patients. This is thought to be a function of inhibition of calcium transport across the platelet membrane. No clinical significance for these findings has been demonstrated.

Positive Direct Coombs test with/without hemolytic anemia has been reported but a causal relationship between nifedipine administration and positivity of this laboratory test, including hemolysis, could not be determined.

Although nifedipine has been used safely in patients with renal dysfunction and has been reported to exert a beneficial effect in certain cases, rare reversible elevations in BUN and serum creatinine have been reported in patients with pre-existing chronic renal insufficiency. The relationship to nifedipine therapy is uncertain in most cases but probable in some.
Drug Interactions—Beta-adrenergic blocking agents: (See WARNINGS) Experience in over 1400 patients with Procardia® capsules in a noncomparative clinical trial has shown that concomitant administration of nifedipine and beta-blocking agents is usually well tolerated but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension, or exacerbation of angina.

Long Acting Nitrates: Nifedipine may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Digitalis: Administration of nifedipine with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with coronary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing nifedipine to avoid possible over- or under-digitalization.

Coumarin Anticoagulants: There have been rare reports of increased prothrombin time in patients taking coumarin anticoagulants to whom nifedipine was administered. However, the relationship to nifedipine therapy is uncertain.

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak nifedipine plasma levels (80%) and area-under-the-curve (74%), after a one week course of cimetidine at 1000 mg per day and nifedipine at 40 mg per day. Ranitidine produced smaller, non-significant increases. The effect may be mediated by the known inhibition of cimetidine on hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of nifedipine. If nifedipine therapy is initiated in a patient currently receiving cimetidine, cautious titration is advised.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Nifedipine was administered orally to rats, for two years and was not shown to be carcinogenic. When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose. *In vivo* mutagenicity studies were negative.
Pregnancy: Pregnancy Category C. Nifedipine has been shown to be teratogenic in rats when given in doses 30 times the maximum recommended human dose. Nifedipine was embryotoxic (increased fetal resorptions, decreased fetal weight, increased stunted forms, increased fetal deaths, decreased neonatal survival) in rats, mice, and rabbits at doses of from 3 to 10 times the maximum recommended human dose. In pregnant monkeys, doses 2/3 and twice the maximum recommended human dose resulted in small placentas and underdeveloped chorionic villi. In rats, doses three times maximum human dose and higher caused prolongation of pregnancy. There are no adequate and well controlled studies in pregnant women. PROCARDIA XL® (nifedipine) Extended Release Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
ADVERSE EXPERIENCES: Over 1000 patients from both controlled and open trials with PROCARDIA XL Extended Release Tablets in hypertension and angina were included in the evaluation of adverse experiences. All side effects reported during PROCARDIA XL Extended Release Tablet therapy were tabulated independent of their causal relation to medication. The most common side effect reported with PROCARDIA XL was edema which was dose related and ranged in frequency from approximately 10% to about 30% at the highest dose studied (180 mg). Other common adverse experiences reported in placebo-controlled trials include: headache (15.8%, compared to 9.8% placebo incidence), fatigue (5.9%, compared to 4.1% placebo incidence), dizziness (4.1%, compared to 4.5% placebo incidence), constipation (3.3%, compared to 2.3% placebo incidence), and nausea (3.3%, compared to 1.9% placebo incidence). Of these, only edema and headache were more common in PROCARDIA XL patients than placebo patients.

The following adverse reactions occurred with an incidence of less than 3.0%. With the exception of leg cramps, the incidence of these side effects was similar to that of placebo alone: *body as a whole/systemic:* asthenia, flushing, pain; *cardiovascular:* palpitations; *central nervous system:* insomnia, nervousness, paresthesia, somnolence; *dermatologic:* pruritus, rash; *gastrointestinal:* abdominal pain, diarrhea, dry mouth, dyspepsia, flatulence; *musculoskeletal:* arthralgia, leg cramps; *respiratory:* chest pain (nonspecific), dyspnea; *urogenital:* impotence, polyuria.

Other adverse reactions were reported sporadically with an incidence of 1.0% or less. These include: *body as a whole/systemic:* face edema, fever, hot flashes, malaise, periorbital edema, rigors; *cardiovascular:* arrhythmia, hypotension, increased angina, tachycardia, syncope; *central nervous system:* anxiety, ataxia, decreased libido, depression, hypertonia, hypoesthesia, migraine, paroniria, tremor, vertigo; *dermatologic:* alopecia, increased sweating, urticaria, purpura; *gastrointestinal:* eructation, gastroesophageal reflux, gum hyperplasia, melena, vomiting, weight increase; *musculoskeletal:* back pain, gout, myalgias; *respiratory:* coughing, epistaxis, upper respiratory tract infection, respiratory disorder, sinusitis; *special senses:* abnormal lacrimation, abnormal vision, taste perversion, tinnitus; *urogenital/reproductive:* breast pain, dysuria, hematuria, nocturia.

Adverse experiences which occurred in less than 1 in 1000 patients cannot be distinguished from concurrent disease states or medications.

In multiple-dose U.S. and foreign controlled studies with nifedipine capsules in which adverse reactions were reported spontaneously, adverse effects were frequent but generally not serious and rarely required discontinuation of therapy or dosage adjustment. Most were expected consequences of the vasodilator effects of Procardia. Adverse experiences reported in placebo-controlled trials include: dizziness, lightheadedness, and giddiness (27%, compared to 15% placebo incidence); flushing, heat sensation (25%, compared to 8% placebo incidence); headache (23%, compared to 20% placebo incidence); weakness (12%, compared to 10% placebo incidence); nausea, heartburn (11%, compared to 8% placebo incidence); muscle cramps, tremor (8%, compared to 3% placebo incidence); peripheral edema (7%, compared to 1% placebo incidence); nervousness, mood changes (7%, compared to 4% placebo incidence); palpitation (7%, compared to 5% placebo incidence); dyspnea, cough, and wheezing (6%, compared to 3% placebo incidence); and nasal congestion, sore throat (6%, compared to 8% placebo incidence).

There is also a large uncontrolled experience in over 2100 patients in the United States. Most of the patients had vasospastic or resistant angina pectoris, and about half had concomitant treatment with beta-adrenergic blocking agents. The relatively common adverse events were similar in nature to those seen with PROCARDIA XL.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

In a subgroup of over 1000 patients receiving Procardia with concomitant beta blocker therapy, the pattern and incidence of adverse experiences was not different from that of the entire group of Procardia treated patients (See PRECAUTIONS.)

In a subgroup of approximately 250 patients with a diagnosis of congestive heart failure as well as angina, dizziness or lightheadedness, peripheral edema, headache or flushing each occurred in one in eight patients. Hypotension occurred in about one in 20 patients. Syncope occurred in approximately one patient in 250. Myocardial infarction or symptoms of congestive heart failure each occurred in about one patient in 15. Atrial or ventricular dysrhythmias each occurred in about one patient in 150.

More detailed professional information available on request.

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Usefulness of Coronary Angioplasty in Asymptomatic Patients

H. Vernon Anderson, MD, J. David Talley, MD, Alexander J. R. Black, MBBS, Gary S. Roubin, MBBS, PhD, John S. Douglas, Jr., MD, and Spencer B. King, III, MD

Of 6,545 patients who had elective coronary angioplasty procedures performed over a 7.5-year period from June 1980 through December 1987, 114 (1.7%) never had symptoms of myocardial ischemia. Exercise-induced silent myocardial ischemia was documented before angioplasty in 94% of these asymptomatic patients. Angioplasty was successful in 87%, whereas emergency coronary artery bypass grafting was required in 4%, and a further 2% had myocardial infarctions after the procedures. The remaining 7% had unsuccessful angioplasty procedures but experienced no in-hospital cardiac events. The follow-up period after hospital discharge averaged 43 ± 20 months (range 5 to 93). There were no deaths. In the group of 99 patients with initially successful angioplasty procedures the follow-up interval ranged from 5 to 92 months. During that period, 7 patients underwent coronary bypass surgery, 4 patients had myocardial infarction and 30 patients had repeat angioplasty procedures for restenosis. The cumulative probability of event-free survival over 5 years for the group with successful angioplasty was: 100% freedom from death, 95% freedom from myocardial infarction, 87% freedom from myocardial infarction or coronary bypass surgery and 61% freedom from myocardial infarction, coronary bypass surgery or repeat angioplasty. Thus, coronary angioplasty performed in 114 asymptomatic patients, most with exercise-induced silent myocardial ischemia, achieved very good primary success and was accompanied by low cardiac event rates and no deaths over several years of patient follow-up.

(Am J Cardiol 1990;65:35–39)

Optimal therapy for patients with asymptomatic coronary artery disease is not resolved. Abolition of anginal episodes in those patients who have them is a standard goal of medical regimens. Whether this abolishes all or only some of the ischemic episodes is unclear, and the prognostic importance of asymptomatic ischemic episodes is still uncertain but may not be favorable.[1–4] Although indications for coronary angioplasty have expanded markedly, it is still used predominantly to treat symptomatic ischemic coronary disease.[5] We review short- and long-term results of coronary angioplasty in patients with coronary artery disease who had never been symptomatic.

METHODS

Study patients: From July 1980 through December 1987, 6,545 patients had elective coronary angioplasty procedures performed at Emory University Hospital. Baseline clinical data were collected prospectively for all patients. There were 114 patients (1.7%) identified as not having any angina pectoris or myocardial infarction before the procedure. The records of these patients were reviewed to confirm the absence of symptomatic coronary artery disease.

Angiographic and procedural variables: Luminal diameter stenosis of coronary arterial lesions was measured with an electronic digital caliper system. Stenosis of ≥50% was considered significant. Multivessel disease was defined as significant stenosis in ≥2 major epicardial arteries or their large branches: either left anterior descending, left circumflex or right coronary artery.

Angioplasty was performed in the standard manner. Success was defined as residual stenosis <50% at all sites attempted without the occurrence of death, myocardial infarction or emergency coronary artery bypass graft surgery.

Data collection and follow-up: Clinical, angiographic and procedural data were prospectively recorded on standard forms and entered into a computer database. Additional data regarding clinical status, presence of risk factors for coronary artery disease, medications and performance of exercise tolerance testing were obtained. If exercise testing had not been performed, the reason for diagnostic cardiac catheterization was determined. These supplemental data were added to the database. Follow-up information was obtained by mail questionnaire and telephone interview. All 114 patients or their physicians were contacted. This information was also added to the database.

Statistical analysis: Continuous variables were analyzed with unpaired *t* tests or 1-factor analysis of variance. Categorical variables were analyzed with chi-

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Address for reprints: Spencer B. King, III, MD, Andreas Gruentzig Cardiovascular Center, F-606 Emory Hospital, 1364 Clifton Road, Atlanta, Georgia 30322.

TABLE I Clinical, Angiographic and Procedural Characteristics of 114 Asymptomatic Patients

Age (yrs) (mean ± SD)	57 ± 9
Male sex (%)	111 (97)
Hypertension (%)	51 (44)
Diabetes mellitus (%)	7 (6)
Cigarette smoking (%)	
Never	39 (34)
Former/current	75 (66)
Medications (%)	
β blockers	38 (33)
Calcium antagonists	8 (7)
Antihypertensives	31 (27)
Detection (%)	
Exercise test	107 (94)
General physical	61 (54)
Risk factors	29 (25)
Executive	10 (9)
Pilot	7 (6)
No exercise test	7 (6)
Coronary vessel dilated (%)	
Left anterior descending	66 (58)
Left circumflex	12 (10)
Right	36 (32)
Multivessel disease (%)	35 (31)
Multivessel dilatation (%)	11 (10)
Multisite dilatation (%)	22 (19)
Calcified lesion (%)	10 (9)
Eccentric lesion (%)	61 (54)
Intimal dissection (%)	47 (41)
Successful angioplasty (%)	99 (87)
Unsuccessful angioplasty (%)	15 (13)
Emergency coronary bypass	5 (4)
Myocardial infarction	2 (2)
No event	8 (7)

SD = standard deviation.

square or Fisher exact tests. Event-free survival was calculated and plotted according to the Kaplan-Meier method. A p value ≤ 0.05 was considered significant.

RESULTS

Patient characteristics: The clinical, angiographic and procedural characteristics of the 114 asymptomatic patients are listed in Table I. Most were men, <50% had systemic hypertension and two-thirds were current or former cigarette smokers. Only 6% had diabetes mellitus. Fifty-four patients (47%) were taking ≥1 cardiovascular medication at the time of diagnostic catheterization. Thirty-three percent were receiving β-blocking agents, 7% were receiving calcium antagonists and approximately 25% were receiving other antihypertensive medicines.

Detection: One hundred seven patients (94%) had positive screening exercise tests that initiated diagnostic cardiac catheterization. In 61 patients (54%), the exercise tests were performed as part of general age-related or life insurance-related physical examinations. In 29 patients (25%) exercise tests were performed because of the presence of risk factors, even though the patients had no symptoms. Another 7 patients were commercial airline pilots undergoing routine flight-certification physical examinations, whereas 10 patients were executives having company-sponsored annual physical examinations.

In 7 patients (6%), no exercise tests were performed. These patients underwent diagnostic cardiac catheterization for a variety of reasons. Four asymptomatic patients had strong family histories of coronary artery disease and the presence of other risk factors. Two patients had nonspecific ST-T wave changes on routine resting electrocardiograms before operative procedures: 1 patient before aortic aneurysm repair; 1 patient before prostate resection. One other patient had complex ventricular ectopy noted on a resting electrocardiogram made during a routine physical examination.

Coronary disease and angioplasty success: Multivessel disease was present in almost one-third of these patients. Multivessel dilatation was performed in 10% and multisite dilatation was performed in 19%. Intimal dissection at dilated sites occurred in 41% of the group.

Successful dilatation of all sites attempted was achieved in 99 (87%) of the 114 patients. In 15 patients (13%), angioplasty was not successful: 5 patients (4%) required emergency coronary bypass surgery, 2 patients (2%) sustained myocardial infarctions and in the remaining 8 patients (7%) the attempted lesions could not be crossed or were not sufficiently reduced although the patients had no in-hospital cardiac events. The only significant differences between the group with successful angioplasty and the unsuccessful group were a greater incidence of calcified lesions (33 vs 5%, $p < 0.01$) and shorter mean lesion length (3.5 ± 1.9 vs 6.8 ± 4.2 mm, $p < 0.05$) in the unsuccessful group.

Follow-up: All 114 patients had follow-up contacts. The mean length of follow-up was 43 ± 20 months (range 5 to 93). The 5 patients who underwent emergency coronary bypass surgery for unsuccessful angioplasty were alive and had not experienced further cardiac events (myocardial infarction, repeat bypass surgery or repeat angioplasty). Similarly, both patients who had myocardial infarctions were alive and without further cardiac events. Eight patients had unsuccessful procedures but no in-hospital cardiac events. One of these patients later suffered myocardial infarction and 2 underwent coronary bypass surgery during 13 to 66 months of follow-up; 5 of these 8 patients experienced no cardiac events. In 99 patients with successful procedures, the follow-up period ranged from 5 to 92 months. During this time, there were no deaths, whereas 4 patients had myocardial infarctions, 7 patients underwent coronary bypass surgery and 30 patients had repeat coronary angioplasty procedures. Combining these cardiac events for the group with successful procedures, 9 patients had either myocardial infarctions or coronary bypass surgery, and 34 patients had either myocardial infarction, coronary bypass surgery or repeat angioplasty during follow-up. Event-free survival for the entire group of 114 patients and for the 99 patients with successful coronary angioplasty is shown in Figure 1.

DISCUSSION

Coronary artery disease may exist with or without angina pectoris, and with or without objective evidence of myocardial ischemia.[6,7] A growing body of data suggests that substantial myocardial ischemia may be detected at times in the absence of angina.[8–11] The pathophysiologic mechanisms for this are poorly understood and controversial, but may include neurosensory abnor-

malities or alterations in vasoreactivity possibly based on smoking, mental stress, cold provocation and circadian factors.[7]

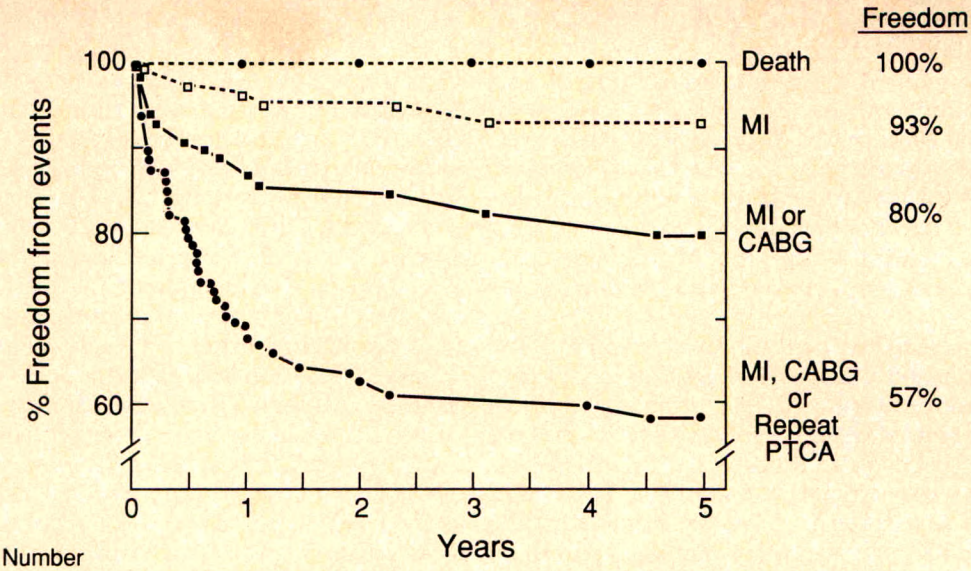
Event-free survival in patients with coronary artery disease is related to the extent of disease as well as to left ventricular function.[12,13] The presence or absence of provocable myocardial ischemia also is prognostically significant,[14] whereas presence or absence of angina may not be. Patients with coronary artery disease may be at higher risk for cardiac events if they have ischemia regardless of whether that ischemia produces angina.

Assey et al[15] reported on the follow-up in 55 patients with angiographically documented coronary artery disease and positive exercise thallium scintigrams. Myocardial infarction or death occurred in 33% of the patients with asymptomatic ischemia but in only 4% of those patients with symptomatic ischemia. The symptomatic patients received more intense medical therapy, particularly with nitrates, perhaps contributing to their better event-free survival. Falcone et al[16] reported the follow-up of 473 patients with angiographically documented coronary disease and positive exercise treadmill electrocardiograms. The group of 269 patients with symptoms as well as positive exercise tests had coronary bypass surgery performed almost twice as frequently as the group of 204 patients with asymptomatic positive exercise tests (45 vs 24%). However, 156 symptomatic patients and 156 asymptomatic patients were treated medically. Survival over 6 years was no different (approximately 90%) in these 2 groups. Thus, even in these presumably lower-risk subsets of patients, there was no survival benefit when symptoms were absent compared to when symptoms were present, if the exercise electrocardiogram indicated ischemia. Similarly, Weiner et al[17] examined long-term survival in patients in the Coronary Artery Surgery Study Registry. The 7-year survival in 424 patients with asymptomatic positive exercise treadmill electrocardiograms was 76%, essentially equal to the 78% survival in 456 patients who had symptoms along with positive exercise tests. Furthermore, the incidence of myocardial infarction during follow-up was equal in the 2 groups.[18] Finally, Dagenais et al[19] reported follow-up over 6 years in 298 patients with positive exercise treadmill electrocardiograms. Patients without symptoms but with positive exercise tests had slightly but significantly better overall survival than patients who had symptoms along with positive exercise tests (85 vs 80%, $p < 0.05$). However, the incidence of sudden death during follow-up was 7% in both asymptomatic and symptomatic groups. Thus, a substantial body of data exists to suggest that asymptomatic ischemic coronary artery disease may not be a benign entity.

Therapy: The treatment of asymptomatic patients with coronary artery disease remains unclear. Indeed, the goal of most medical regimens is to make patients asymptomatic. The reduction or elimination of all ischemia, symptomatic or silent, is gaining increasing attention.[1] Whether this will improve event-free survival is not known. Likewise, the role of coronary angioplasty in the treatment of asymptomatic patients with coronary disease is unknown but is now beginning to be explored. Josephson et al[20] found that successful coronary angioplasty eliminated Holter monitor-detected ischemia in 10 patients with such ischemia before the procedure. No long-term follow-up to examine sustained elimination of this ischemia has been reported. Finci et al[21] performed coronary angioplasty in 50 asymptomatic patients, achieving success in 92%. Follow-up averaged 12 ± 6 months. There were no deaths and there was 1 myocardial infarction, whereas restenosis occurred in 32% of 41 patients undergoing follow-up catheterization. Bergin et al[22] performed coronary angioplasty in 54 asymptomatic patients, with success in 89%. Follow-up ranged from 5 to 85 months (mean 35). There were no deaths. Among the 48 successfully dilated patients, 9 (19%) had restenosis and 3 developed new disease, so that 12 patients had repeat angioplasty procedures. In that group, there was 1 emergency coronary bypass after the repeat angioplasty attempt and 1 late myocardial infarction. Forty-six of the initially successful 48 patients (96%) had no other cardiac events.

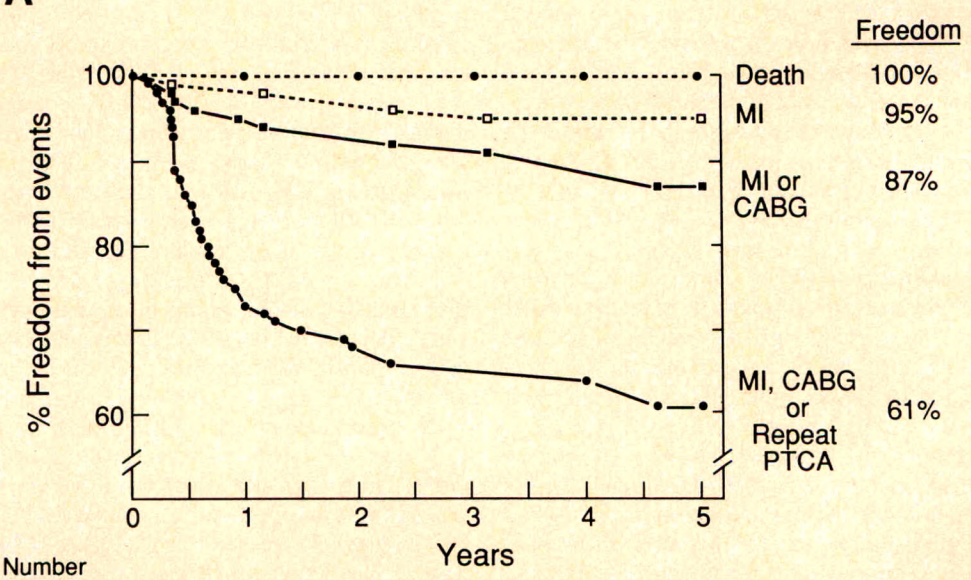
Cohn[7] has proposed a classification system for patients with coronary artery disease and asymptomatic myocardial ischemia. Type 1 patients are completely asymptomatic; type 2 patients are asymptomatic after a myocardial infarction; and type 3 patients have both angina and silent myocardial ischemia. Although the usefulness of this classification system remains to be determined, it is widely known. It may be possible that type 1 patients have uniformly good prognosis without therapy and that angioplasty offers no benefit. Very little data exist on this point. Hickman et al[23] reported 3-year follow-up in 78 type 1 men. During that interval, myocardial infarction occurred in 5% and sudden death in 4% of the group. Erikssen and Thaulow[24] reported 8-year follow-up of 50 type 1 men. Myocardial infarction occurred during follow-up in 14%, another 22% underwent coronary bypass surgery and 6% died. By 12 years, the mortality in this group of 50 patients was 24%.[25] Thus, at least in these 2 small studies, type 1 patients had substantial cardiac event rates during long-term observation.

We examined short- and long-term results of coronary angioplasty in 114 consecutive asymptomatic patients. Patients in our study were overwhelmingly type 1: 94% were asymptomatic with positive exercise tests and no prior evidence of cardiac disease. This is in contrast to the findings of Finci et al,[21] where 69% were type 1, and to Bergin et al,[22] where only 10% were type 1. Successful dilatation was accomplished in 87% of our patients, and over a mean follow-up of 43 months there were no deaths in either successful or unsuccessful angioplasty patients. This is consistent with Finci et al,[21] and Bergin et al,[22] who achieved success in 92 and 89% of attempted patients, respectively, and both groups noted no mortality during follow-up. In our group of 99 patients with successful angioplasty procedures the incidence of myocardial infarction during follow-up was 4%, exactly the same noted by Bergin et al,[22] who also had a similar follow-up interval. Fully 30% of our successfully dilated patients had repeat procedures for restenosis, similar to the 32% restenosis rate noted by



Number at Risk					
Death	108	82	68	50	19
MI	104	78	64	46	19
MI or CABG	95	72	59	43	18
MI, CABG or Repeat PTCA	76	54	43	32	13

A



Number at Risk					
Death	94	73	59	43	18
MI	93	71	57	41	18
MI or CABG	90	67	55	40	17
MI, CABG or Repeat PTCA	70	50	39	29	12

B

FIGURE 1. Event-free survival curves after coronary angioplasty for asymptomatic patients with coronary artery disease. *A*, event-free survival for entire group of 114 asymptomatic patients. *B*, event-free survival for group of 99 asymptomatic patients with successful angioplasty procedures. The tables below each graph show number of patients at risk for events at end of each year. CABG = coronary artery bypass graft surgery; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

Finci et al.[21] As mentioned earlier, patients in these 3 studies may not be comparable because there were different proportions of patients with prior myocardial infarction, prior bypass surgery and prior symptom status.

Limitations: The protocol at our institution is to recommend follow-up angiography 6 months after angioplasty unless clinical indications suggest it be done earlier. Exercise testing is not a routine component of our follow-up, and it was not consistently performed in these patients even though exercise testing was the initial method of diagnosis in most of them. This correlative information on exercise testing and restenosis would be quite useful. Two other limitations of this study are the relatively small number of patients analyzed and the lack of a concurrent control group. We cannot exclude the possibilities that the absence of mortality and the low rate of myocardial infarction in our patients were due to selection bias, occurred by chance or perhaps reflected an inherently low rate of cardiac events in this population. Further studies that randomize asymptomatic patients with coronary artery disease into various treatment arms will be required to fully investigate these issues.

Acknowledgment: We thank Cynthia Sutor, RN, for technical assistance, Sufen Lin for computer programming assistance and Debbie Shuttlesworth for manuscript preparation.

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Treatment of Ventricular Arrhythmias by United States Cardiologists: a Survey Before the Cardiac Arrhythmia Suppression Trial Results Were Available

Joel Morganroth, MD, J. Thomas Bigger, Jr., MD, and Jeffrey L. Anderson, MD

To define the practice habits of United States cardiologists and the treatment of ventricular arrhythmias, a random sample of 1,000 of 12,000 cardiologists was sent a pretested questionnaire. After follow-up procedures, 252 responded, of which 18% were academically-based, 29% were hospital-based and 53% were office-based. Attitudes about antiarrhythmic drug therapy for the treatment of ventricular arrhythmias were influenced by the presence and severity of cardiac disease, the presence of symptoms and the type of ventricular arrhythmias. In this survey, only 1% of cardiologists treated patients with asymptomatic ventricular premature complexes and no heart disease, but 17% treated such patients if unsustained ventricular tachycardia was present. The treatment rate among cardiologists increased to 38% when coronary artery disease with left ventricular dysfunction was present in patients with asymptomatic ventricular premature complexes. The presence of any cardiac disease and symptomatic ventricular arrhythmias increased the treatment rate to 80 to 100%. Approximately 50% of responding physicians treated patients comparable to the Cardiac Arrhythmia Suppression Trial study population with antiarrhythmic drugs. Beta blockers were the most common antiarrhythmic drug class chosen as the most appropriate initial therapy in new patients with ventricular arrhythmias. Whereas no cardiologists thought that amiodarone was appropriate to initiate in new patients with benign or potentially malignant ventricular arrhythmias, as many as 33 to 43% of cardiologists would use amiodarone for refractory patients with such arrhythmias, a response contradictory to the approved labeling for this drug.

Less than one half of cardiologists recognize the high potential organ toxicity for quinidine, procainamide and tocainide. Cardiologists believed that antiarrhythmic agents with class IA and IC action were equally proarrhythmic in patients with potentially malignant ventricular arrhythmias. Antiarrhythmic drugs were initiated only in-hospital by about 25 to 50% of cardiologists. Electrophysiologic testing was always used by 63% of cardiologists for evaluation of sustained ventricular tachycardia; 33% never used such testing for patients with potentially malignant ventricular arrhythmias. There were no differences in these results based on the geographic location of the responding cardiologists.

Thus, significant lack of consensus exists on the toxicity of antiarrhythmic drugs, use of electrophysiologic testing and in- versus out-of-hospital drug initiation. At the time of the survey, most cardiologists treated patients with asymptomatic and symptomatic potentially malignant ventricular arrhythmias, although the interim results of the Cardiac Arrhythmia Suppression Trial indicate reconsideration for therapy in such patients.

(Am J Cardiol 1990;65:40–48)

Although a consensus exists about the management of patients with either benign or malignant ventricular arrhythmias, the management of the large group of patients with potentially malignant ventricular arrhythmias is controversial.[1,2] An example of the potentially malignant group is the postmyocardial infarction patient with minimally symptomatic or asymptomatic ventricular ectopy. It was hoped that the Cardiac Arrhythmia Suppression Trial (CAST), which began in June 1987, would determine whether antiarrhythmic drug suppression of asymptomatic or mildly symptomatic ventricular premature complexes (VPCs) with or without unsustained ventricular tachycardia (VT) would significantly decrease the arrhythmic death rate.[3] It is expected that the practice patterns of cardiologists will evolve with new information from clinical trials and with the availability of new antiarrhythmic drugs. To measure the practice of United States cardiologists in regard to ventricular arrhythmia management, we conducted a survey before release of the interim results of CAST.

METHODS

The questionnaire: A 4-page questionnaire was developed under the name "National Arrhythmia Survey" to evaluate the indications for treatment of ventricular

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TABLE I Use of Antiarrhythmic Drugs by Patient Group, Arrhythmia Type and Symptoms (% of 252 Cardiologists)

	Asymptomatic		Symptomatic		
Cardiac Status	VPC	VPC + VT-n	VPC	VPC + VT-n	VT-s
No heart disease	1	17	66	88	100
No CAD, LVEF <0.40	21	61	80	96	100
CAD, LVEF >0.40	13	51	80	97	100
CAD, LVEF <0.40	38	76	88	98	100
AMI within 6 months	41	79	90	98	100
Symptomatic CHF	36	73	86	96	100

AMI = acute myocardial infarction; CAD = coronary artery disease; CHF = congestive heart failure; LVEF = left ventricular ejection fraction; VPC = ventricular premature complexes; VT-s = sustained ventricular tachycardia; VT-n = unsustained ventricular tachycardia.

TABLE II Sequence of Antiarrhythmic Drugs by Ventricular Arrhythmia Class in Symptomatic Patients (% of 252 Cardiologists)

	Appropriate to Initiate in New Patients			Not Appropriate for New Patients but Not Reserved for Refractory Cases			Reserved Only for Refractory Cases		
	B	PM	M	B	PM	M	B	PM	M
Quinidine	68	78	90	20	15	7	7	3	1
Procainamide	65	78	90	23	16	7	6	3	1
Disopyramide	42	53	64	36	28	22	12	10	4
Mexiletine	45	53	93	34	32	6	12	9	0
Tocainide	31	41	47	31	29	26	15	13	14
Encainide	42	51	61	35	33	29	16	11	6
Flecainide	39	45	59	35	37	29	18	13	8
β blockers	80	80	38	11	12	26	2	1	1
Amiodarone	0	0	7	4	6	14	33	43	76

B = benign; M = malignant; PM = potentially malignant.

TABLE III Ratings of the Efficacy of Antiarrhythmic Drugs for Potentially Malignant or Malignant Ventricular Arrhythmias (% of 252 Cardiologists)

	Potentially Malignant				Malignant			
	High	Moderate	Low	?	High	Moderate	Low	?
Quinidine	34	60	6	0	28	57	14	1
Procainamide	36	59	5	0	30	57	13	0
Disopyramide	18	67	13	2	11	58	27	4
Mexiletine	26	49	23	2	20	44	33	3
Tocainide	15	52	29	4	13	42	41	4
Encainide	65	26	4	5	40	43	11	6
Flecainide	73	21	3	3	45	39	12	4
β blockers	8	37	54	1	3	17	78	2
Amiodarone	71	7	3	19	85	9	1	4

? = don't know.

TABLE IV Ratings of the Noncardiac Adverse Effects of Antiarrhythmic Drugs (% of 252 Cardiologists)

	Adverse Effects				Organ Toxicity			
	High	Medium	Low	?	High	Medium	Low	?
Quinidine	70	24	6	0	31	38	31	0
Procainamide	54	38	8	0	40	38	31	0
Disopyramide	65	25	10	0	21	23	54	2
Mexiletine	39	43	14	4	9	32	55	4
Tocainide	59	30	5	6	37	31	28	4
Encainide	15	41	39	5	6	31	57	6
Flecainide	17	43	36	4	13	29	54	4
β blockers	37	39	24	0	2	17	81	0
Amiodarone	94	3	1	2	95	2	1	2

? = don't know.

arrhythmias based on the presence and degree of heart disease, symptoms and type of arrhythmia. The questionnaire provided specific definitions for arrhythmia classification and for symptoms. In addition, the currently available antiarrhythmic drugs approved by the Food and Drug Administration in the United States were listed alphabetically in the questionnaire (although reported herein by antiarrhythmic class). We sought to determine cardiologists' attitudes about indications for treatment and the relative degrees of efficacy, noncardiac adverse effects, probability of organ toxic effects, proarrhythmia and negative inotropic features of antiarrhythmic drugs. Information also was obtained on how cardiologists used electrophysiologic testing in their practice.

We pretested the questionnaire using 20 cardiologists and revised the questionnaire based on this pretest to enhance its clarity (Appendix). A marketing research firm, Anderson, Neibuhr and Associates, handled the logistics of mailing the questionaires and data tabulation.

Population sample, data collection and analysis: A list of approximately 12,000 actively practicing cardiologists represented the initial database for selection of the sample population. From the list, a random sample of 1,000 cardiologists was selected by a digital computer. The survey was conducted from May to November 1988. The questionnaire was sent to the 1,000 cardiologists with a cover letter by first class mail with a preaddressed postage-paid return envelope. Cardiologists who did not respond were sent 3 additional follow-up reminders with a second copy of the questionnaire. An option for a telephone interview to complete the survey also was offered. The completed surveys were transferred to magnetic tape for computer analysis and were quality controlled for data verification. The Statistical Package for the Social Sciences was used in the analysis.

RESULTS

Questionnaires were returned by 252 of the 1,000 cardiologists sampled (25%). Generalization of the data to all cardiologists should be performed cautiously due to this response rate. Of the cardiologists responding, 53% said their practice was office-based, 29% were hospital-based and 18% were academically-based. Twenty-

TABLE V Ranking of Major Cardiovascular Adverse Effects of Antiarrhythmic Drugs (% of 252 Cardiologists)

	Proarrhythmia in Patients with Potentially Malignant Ventricular Arrhythmias				Proarrhythmia in Patients with Malignant Ventricular Arrhythmias				Aggravation of Congestive Heart Failure			
	High	Mod	Low	?	High	Mod	Low	?	High	Mod	Low	?
Quinidine	38	42	19	1	46	42	10	2	11	44	43	2
Procainamide	24	50	25	1	35	51	12	2	9	52	37	2
Disopyramide	16	48	33	3	37	44	14	5	88	9	1	2
Mexiletine	12	42	42	4	18	46	29	7	5	38	53	4
Tocainide	12	39	42	7	18	45	29	8	5	37	51	7
Encainide	33	45	19	3	54	36	6	4	18	45	33	4
Flecainide	43	39	16	2	57	22	5	3	64	25	9	2
β blockers	2	12	85	1	15	23	55	7	88	6	2	1
Amiodarone	14	29	45	12	20	32	37	11	14	37	43	6

Mod = moderate; ? = don't know.

one percent of the respondents lived in the Western United States, 26% in the Midwest, 23% in the Northeast and 30% in the South.

Table I lists the cardiologists' responses to the survey's first question, in which their decisions to use antiarrhythmic therapy were related to the presence and severity of cardiac disease, type of arrhythmia and degree of symptoms. Whereas 1% of cardiologists routinely prescribed antiarrhythmic drugs for patients without heart disease and asymptomatic VPCs, 17% treated such patients if unsustained VT was present. In asymptomatic patients, the type of ventricular arrhythmia and the severity of cardiac disease were each of approximately equal importance in treatment decisions (columns 3 and 4 in Table I). When symptoms and heart disease were present, >80% of cardiologists gave treatment. The questionnaire subgroups that relate closely to the patient population being studied in the CAST are those with acute myocardial infarction within 6 months or coronary artery disease with ejection fraction <0.40 (columns 4 and 5 in Table I). Antiarrhythmic agents were used in this population by 38 to 98% of cardiologists, with an estimated overall treatment rate of about 50%.

Table II lists the responses for questions 2, 3 and 4 in the survey, in which the first drug chosen for antiarrhythmic therapy in symptomatic patients is related to the classification of ventricular arrhythmias. Symptomatic ventricular arrhythmias without cardiac disease were considered benign, whereas frequent VPCs or unsustained VT with coronary heart disease or congestive heart failure were considered to be potentially malignant. Documented sustained ventricular arrhythmias were classified as malignant.[1,2] In patients with benign ventricular arrhythmias, β blockers were clearly the most common antiarrhythmic drug chosen or selected to start treatment. Cardiologists were divided in opinion regarding the use of class IA, IB and IC antiarrhythmic drugs as initial therapy.[4]

In patients with potentially malignant ventricular arrhythmias, β blockers were again the most commonly selected group for initial therapy. Older, more familiar drugs such as quinidine and procainamide were ranked ahead of class IB and IC drugs. Responding cardiologists considered amiodarone inappropriate to initiate in new patients with benign or potentially malignant arrhythmias. As many as 33 to 43% of cardiologists thought that amiodarone was appropriate, however, for refractory cases with benign or potentially malignant ventricular arrhythmias despite the fact that the Food and Drug Administration approval for amiodarone is limited to patients with malignant ventricular arrhythmias when other antiarrhythmic agents have failed.

In patients with malignant ventricular arrhythmias, quinidine and procainamide were ranked first for initiation of therapy. Mexiletine also was ranked strikingly high, substantially higher than tocainide, perhaps related to its frequent combined use with quinidine or procainamide and the perception of its lower organ toxicity. Although encainide and flecainide are generally reserved for patients refractory to drugs with class IA and IB antiarrhythmic action, about 60% of cardiologists thought that encainide and flecainide were appropriate to use as initial therapy in patients with malignant ventricular arrhythmias.

Table III lists responses to questions 5 and 6 in the survey and defines the cardiologists' opinions about the relative efficacy of antiarrhythmic drugs for patients with potentially malignant and malignant arrhythmias. The opinions on efficacy are generally consistent with the efficacy results in previous reviews.[5] Although 80% of cardiologists thought it was appropriate to use β blockers as initial therapy in new patients with potentially malignant arrhythmias (Table II), only 8% thought that they were highly efficacious and 54% thought that they had low efficacy (Table III). Morganroth[6] suggests that β blockers are effective in approximately 50% of such patients. Although amiodarone is not indicated for patients with potentially malignant ventricular arrhythmias, 71% of cardiologists rated it as highly efficacious. As expected, the drugs with class IC antiarrhythmic action, encainide and flecai-

nide, were rated as having the highest efficacy in patients with potentially malignant ventricular arrhythmias, followed by procainamide and quinidine, and then by mexiletine, disopyramide and tocainide. In malignant ventricular arrhythmias, amiodarone was rated as the most efficacious. This was followed by the drugs with class IC antiarrhythmic action, then procainamide and quinidine. Mexiletine, tocainide and disopyramide were rated as highly effective by fewer than 21% of responders.

Table IV lists responses to questions 7 and 8 in the survey, which involved the noncardiac safety profile, including adverse effects and organ toxicity for the various antiarrhythmic drugs. Amiodarone was ranked most frequently by cardiologists as having high noncardiac adverse effect potential, followed by quinidine, disopyramide, tocainide and then procainamide. Mexiletine and β blockers were perceived as having little adverse potential by an intermediate percentage. Fewer than 20% of the cardiologists indicated that encainide and flecainide had the potential for a high noncardiac adverse effect rate.

Amiodarone was viewed as having the highest potential for organ toxicity. Beta blockers, encainide, mexiletine and flecainide were least viewed as having a high organ toxic potential. Procainamide, tocainide and disopyramide were ranked intermediate.

Table V lists the answers to questions 9, 10 and 11 in the survey, which assess attitudes about the cardiac safety profile of the antiarrhythmic drugs, such as the potential for proarrhythmia and negative inotropic effect. Proarrhythmic potential is separated by potentially malignant versus malignant ventricular arrhythmias. Cardiologists ranked flecainide, quinidine and encainide as having a high potential for causing proarrhythmia in patients with potentially malignant or malignant ventricular arrhythmias. They ranked procainamide and disopyramide next. Beta blockers were least often perceived to have a high proarrhythmic risk.

Disopyramide and β blockers were most often selected as drugs with a high potential to aggravate heart failure (negative inotropic effect), followed closely by flecainide. Mexiletine, tocainide, procainamide, quinidine and amiodarone were ranked least often as having a high negative inotropic potential, and most often as having a low potential.

Table VI lists the response to question number 12 in the survey, which assessed attitudes on whether antiarrhythmic agents should be initiated in-hospital for patients with potentially malignant ventricular arrhythmias. The survey suggested a lack of consensus on initiation of antiarrhythmic drugs to in- versus outpatients. Only 4% of cardiologists thought that β blockers required initiation in the hospital for patients with potentially malignant ventricular arrhythmias. The drugs that most cardiologists (33 to 44% of responders) thought should be initiated only to in-patients were flecainide, amiodarone, encainide and quinidine. Overall, for antiarrhythmic drugs, about two-thirds of cardiologists initiate them in either the in- or out-patient setting, presumably depending on the nature of the patient's cardiac status. Amiodarone, according to its approved indications, should only be used for malignant ventricular arrhythmias and should always be initiated in-hospital. Of the cardiologists responding to this survey, 44% initiated amiodarone only to in-patients, but 12% chose to initiate amiodarone to either in- or out-patients.

TABLE VI Location Where Antiarrhythmic Drugs Should Be Started for Patients with Potentially Malignant Ventricular Arrhythmias (% of 252 Cardiologists)

	Only In-Patient	In- or Out-Patient	Don't Use This Drug
Quinidine	33	65	2
Procainamide	23	76	1
Disopyramide	20	63	17
Mexiletine	20	71	9
Tocainide	14	67	19
Encainide	40	54	6
Flecainide	48	45	7
β blockers	4	91	5
Amiodarone	44	12	44

TABLE VII Use of Electrophysiologic Testing (% of 252 Cardiologists)

Patient Group	Always	Sometimes	Never
No heart disease, no symptoms	1	11	88
No heart disease, symptoms	6	47	47
CAD + VPC & VT-n, without CHF	5	61	34
VPC + VT-n, with CHF	11	71	18
Documented VT-s	63	35	2

CAD = coronary artery disease; CHF = congestive heart failure; VPC = ventricular premature complexes; VT-s = sustained ventricular tachycardia; VT-n = unsustained ventricular tachycardia.

Table VII lists the response to question number 13 of this survey regarding the use of electrophysiologic testing by cardiac status. Only 63% of cardiologists always obtained electrophysiologic testing in patients with documented sustained VT, whereas 5 to 11% did so as a routine in patients with symptomatic benign or potentially malignant arrhythmias. Only 1% of cardiologists responding would always use electrophysiologic testing in patients with asymptomatic benign ventricular arrhythmias. Eighteen to 47% of cardiologists noted that they would never use electrophysiologic testing in patients with symptomatic benign or potentially malignant ventricular arrhythmias.

DISCUSSION

Our survey of a random sample of cardiologists represented a wide geographic distribution and a balance between office versus hospital and academic practices. Approximately 5 years ago, Vlay[7] surveyed 65 university chiefs of cardiology or arrhythmia specialists regarding the indications for the treatment of ventricular arrhythmias. Despite the fact that Vlay's study involved a select group of university cardiologists, the results were remarkably similar to our survey, and also demonstrated a lack of consensus about therapy of the potentially malignant ventricular arrhythmia group.

Our survey revealed a consensus regarding treatment of patients with benign or malignant ventricular arrhythmias, the classes at the "ends of the spectrum." In patients with no heart disease and asymptomatic VPCs, only 1% of cardiologists responding would routinely prescribe an antiarrhythmic agent compared to the 100% response rate for treatment of patients with symptomatic, sustained VT. In patients with asymptomatic VPCs or VPCs and unsustained VT, an increasing frequency of cardiologists in our survey elected to prescribe antiarrhythmic agents, as patients had progressively more advanced cardiac disease, had coexisting unsustained VT or had associated symptoms. The CAST is testing whether patients, 6 days to 2 years after myocardial infarction with a reduced ejection fraction, mildly symptomatic or asymptomatic VPCs or VPCs and unsustained VT, will benefit from suppression of the ventricular arrhythmias using antiarrhythmic agents. Our survey demonstrated that approximately 50% of responding cardiologists routinely prescribed antiarrhythmic agents to patients comparable to this population. This is similar to results of Vlay's survey,[7] in which 52 to 73% of responding university cardiologists indicated that they would treat asymptomatic patients who had frequent or complex VPCs, in the convalescent phase after acute myocardial infarction. Thus, these 2 surveys, taken approximately 5 years apart, demonstrate a comparably high use of routine antiarrhythmic treatment of such patients in the United States.

In April 1989 the CAST reported that patients receiving encainide or flecainide had a marked increase in the risk of arrhythmic death compared to placebo (relative risk about 2.5).[8] One cannot attribute any individual patient's death to a specific drug. The most appropriate application of these results in medical practice would be not to place asymptomatic patients with recent acute myocardial infarction on antiarrhythmic drug therapy with encainide or flecainide. Whether other or all drugs with class I antiarrhythmic action will act similarly to encainide and flecainide is unknown. However, there is insufficient data to know whether the adverse effect of encainide and flecainide seen in the CAST should be extrapolated to their use in other populations, such as patients with symptomatic ventricular or supraventricular arrhythmias with no heart disease.

In this pre-CAST survey, quinidine was thought by cardiologists to have proarrhythmic rates comparable to encainide and flecainide but with an even higher rate of noncardiac adverse and organ toxic effects (Table V). These responses suggest that it would not be logical for physicians to assume that drugs with class IA action would be ideal substitutes for encainide and flecainide, even in patients with symptomatic ventricular arrhythmias. The increased mortality observed in postmyocardial infarction patients treated with mexiletine,[9,10] and its high rate of noncardiac adverse effects with mexiletine and tocainide would also suggest a reserved judgment for the use of class IB antiarrhythmic agents. It is only the class II drugs, the β-blocking agents, that have demonstrated the potential to reduce total mortality and especially sudden cardiac death in postmyocardial infarction patients.[11] However, β blockers have many effects other than their antiarrhythmic action that may be important to these results. When physicians feel obliged to initiate antiarrhythmic therapy in individual patients, especially in patients after myocardial infarction with potentially malignant ventricular arrhythmias, β-blocking agents continue to appear to be the best choice for first line therapy at present.

The survey also provides information regarding current opinion as to where antiarrhythmic drugs should be initiated (i.e., in- or out-of-hospital). There is clearly no consensus among cardiologists responding to our survey on this issue and there was a particularly wide variation in opinions as to where to initiate antiarrhythmic drugs, especially in patients with potentially malignant ventricular arrhythmias. All patients with hemodynamically unstable malignant ventricular arrhythmias, such as sustained ventricular tachycardia, should have antiarrhythmic drug therapy initiated in-hospital. Conversely, patients with symptomatic benign ventricular arrhythmias usually have antiarrhythmic drugs initiated as outpatients, especially when β blockers are used. Cardiologists were more inclined to initiate in-hospital therapy in patients with more advanced risk of cardiac adverse events that may occur early after therapy and with drugs more likely to be proarrhythmic. Patients with symptomatic congestive heart failure and marked left ventricular dysfunction, such as those with a left ventricular ejection fraction <0.30 or advanced cardiac conduction disease, such as sick-sinus syndrome, or elderly patients with complicating medical problems, would appear to be groups in which in-patient initiation would be more frequently appropriate.

Finally, we addressed indications for the use of electrophysiologic testing in various patient subgroups. Electrophysiologic testing is rarely indicated for patients with benign ventricular arrhythmias, and it appears to have a leading role for evaluating malignant ventricular arrhythmias.[12] The results of our survey emphasize the controversy that exists regarding the indications for electrophysiologic testing in patients with potentially malignant ventricular arrhythmias in whom structural heart disease, VPCs and nonsustained VT exist.[13] We would predict that the results of the CAST may increase the use of signal-averaged electrocardiograms[14] and electrophysiologic testing[15] for risk stratification. Controlled clinical trials will be essential to demonstrate the validity of this rationale.

We document that many factors bearing on the treatment of ventricular arrhythmias (e.g., indications for therapy, which drug is safest and most effective, whether to start treatment in-hospital and how to use electrophysiologic testing) remain controversial. Proper clinical trials such as the CAST are essential to resolve the controversies identified by our survey.

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APPENDIX

NATIONAL ARRHYTHMIA SURVEY

INSTRUCTIONS: It is **important** to use the following definitions when answering this questionnaire. (While they may differ from your own, as a standard, please use these.)

DEFINITIONS:
Frequent VPCs: 10 or more ventricular premature complexes/hour
Unsustained (nonsustained) VT: 3 complexes to 30 seconds, no hemodynamic symptoms (i.e., no syncope or worse)
Sustained VT: 30 or more seconds of ventricular tachycardia, or hemodynamic symptoms (i.e., presyncope or syncope) are present with < 30 seconds of ventricular tachycardia
CHF: Congestive Heart Failure
CHD: Coronary Heart Disease
Symptomatic Ventricular Arrhythmias: Frequent VPCs and Unsustained VT associated with symptoms such as palpitation, dyspnea and fatigue of no hemodynamic consequence.

1. Would you routinely use an antiarrhythmic agent to treat the following types of patients: (Circle yes or no for **each** item)

	Asymptomatic Frequent VPCs		Asymptomatic Unsustained VT and VPCs		Symptomatic Frequent VPCs		Symptomatic Unsustained VT and VPCs		Symptomatic Sustained VT	
a. No heart disease?	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
b. No coronary heart disease with ejection fraction less than 40%?	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
c. Coronary heart disease with ejection fraction greater than 40%?	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
d. Coronary heart disease with ejection fraction less than 40%?	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
e. Myocardial infarction within past six months?	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
f. Symptomatic CHF (NYHA Class III-IV)	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No

FOR ALL REMAINING QUESTIONS, ASSUME YOU WOULD TREAT THE PATIENT.

2. How do you believe the following drugs should be used to treat patients with ***symptomatic* ventricular arrhythmia and no heart disease:** (Check one response for **each** drug)

	Appropriate for initiating therapy in newly diagnosed patients	Not appropriate for newly diagnosed patients but not necessarily reserved only for refractory patients	Should be reserved only for refractory patients	Do not use this drug in this type of patient
a. Amiodarone?	☐	☐	☐	☐
b. Beta-Blockers?	☐	☐	☐	☐
c. Disopyramide?	☐	☐	☐	☐
d. Encainide?	☐	☐	☐	☐
e. Flecainide?	☐	☐	☐	☐
f. Mexiletine?	☐	☐	☐	☐
g. Procainamide?	☐	☐	☐	☐
h. Quinidine?	☐	☐	☐	☐
i. Tocainide?	☐	☐	☐	☐

3. How do you believe the following drugs should be used to treat CHD patients with **frequent VPCs with episodes of unsustained VT with palpitations but no CHF:** (Check one response for **each** drug)

	Appropriate for initiating therapy in newly diagnosed patients	Not appropriate for newly diagnosed patients but not necessarily reserved only for refractory patients	Should be reserved only for refractory patients	Do not use this drug in this type of patient
a. Amiodarone?	☐	☐	☐	☐
b. Beta-Blockers?	☐	☐	☐	☐
c. Disopyramide?	☐	☐	☐	☐
d. Encainide?	☐	☐	☐	☐
e. Flecainide?	☐	☐	☐	☐
f. Mexiletine?	☐	☐	☐	☐
g. Procainamide?	☐	☐	☐	☐
h. Quinidine?	☐	☐	☐	☐
i. Tocainide?	☐	☐	☐	☐

4. How do you believe the following drugs should be used to treat patients with **documented sustained ventricular tachycardia:** (Check one response for **each** drug)

	Appropriate for initiating therapy in newly diagnosed patients	Not appropriate for newly diagnosed patients but not necessarily reserved only for refractory patients	Should be reserved only for refractory patients	Do not use this drug in this type of patient
a. Amiodarone?	☐	☐	☐	☐
b. Beta-Blockers?	☐	☐	☐	☐
c. Disopyramide?	☐	☐	☐	☐
d. Encainide?	☐	☐	☐	☐
e. Flecainide?	☐	☐	☐	☐
f. Mexiletine?	☐	☐	☐	☐
g. Procainamide?	☐	☐	☐	☐
h. Quinidine?	☐	☐	☐	☐
i. Tocainide?	☐	☐	☐	☐

5. How would you rate the **overall efficacy** of the following drugs for treating CHD patients with **frequent VPCs with episodes of unsustained VT but no CHF:** (Check one response for **each** drug)

	Very High Efficacy	High Efficacy	Moderate Efficacy	Low Efficacy	Very Low Efficacy	Don't Know
a. Amiodarone?	☐	☐	☐	☐	☐	☐
b. Beta-Blockers?	☐	☐	☐	☐	☐	☐
c. Disopyramide?	☐	☐	☐	☐	☐	☐
d. Encainide?	☐	☐	☐	☐	☐	☐
e. Flecainide?	☐	☐	☐	☐	☐	☐
f. Mexiletine?	☐	☐	☐	☐	☐	☐
g. Procainamide?	☐	☐	☐	☐	☐	☐
h. Quinidine?	☐	☐	☐	☐	☐	☐
i. Tocainide?	☐	☐	☐	☐	☐	☐

6. How would you rate the **overall efficacy** of the following drugs for treating patients with **documented sustained ventricular tachycardia:** (Check one response for **each** drug)

	Very High Efficacy	High Efficacy	Moderate Efficacy	Low Efficacy	Very Low Efficacy	Don't Know
a. Amiodarone?	☐	☐	☐	☐	☐	☐
b. Beta-Blockers?	☐	☐	☐	☐	☐	☐
c. Disopyramide?	☐	☐	☐	☐	☐	☐
d. Encainide?	☐	☐	☐	☐	☐	☐
e. Flecainide?	☐	☐	☐	☐	☐	☐
f. Mexiletine?	☐	☐	☐	☐	☐	☐
g. Procainamide?	☐	☐	☐	☐	☐	☐
h. Quinidine?	☐	☐	☐	☐	☐	☐
i. Tocainide?	☐	☐	☐	☐	☐	☐

7. How much potential do each of the following drugs have to cause **non-cardiac side effects:** (Circle one response for **each** drug)

	Very High	High	Neither High Nor Low	Low	Very Low	Don't Know
a. Amiodarone?	VH	H	N	L	VL	DK
b. Beta-Blockers?	VH	H	N	L	VL	DK
c. Disopyramide?	VH	H	N	L	VL	DK
d. Encainide?	VH	H	N	L	VL	DK
e. Flecainide?	VH	H	N	L	VL	DK
f. Mexiletine?	VH	H	N	L	VL	DK
g. Procainamide?	VH	H	N	L	VL	DK
h. Quinidine?	VH	H	N	L	VL	DK
i. Tocainide?	VH	H	N	L	VL	DK

8. How much potential do each of the following drugs have to cause **major organ toxicity:** (Circle one response for **each** drug)

	Very High	High	Neither High Nor Low	Low	Very Low	Don't Know
a. Amiodarone?	VH	H	N	L	VL	DK
b. Beta-Blockers?	VH	H	N	L	VL	DK
c. Disopyramide?	VH	H	N	L	VL	DK
d. Encainide?	VH	H	N	L	VL	DK
e. Flecainide?	VH	H	N	L	VL	DK
f. Mexiletine?	VH	H	N	L	VL	DK
g. Procainamide?	VH	H	N	L	VL	DK
h. Quinidine?	VH	H	N	L	VL	DK
i. Tocainide?	VH	H	N	L	VL	DK

9. How much potential do each of the following drugs have to cause **proarrhythmia in patients with frequent VPCs with episodes of unsustained VT but no CHF:** (Circle one response for **each** drug)

	Very High	High	Neither High Nor Low	Low	Very Low	Don't Know
a. Amiodarone?	VH	H	N	L	VL	DK
b. Beta-Blockers?	VH	H	N	L	VL	DK
c. Disopyramide?	VH	H	N	L	VL	DK
d. Encainide?	VH	H	N	L	VL	DK
e. Flecainide?	VH	H	N	L	VL	DK
f. Mexiletine?	VH	H	N	L	VL	DK
g. Procainamide?	VH	H	N	L	VL	DK
h. Quinidine?	VH	H	N	L	VL	DK
i. Tocainide?	VH	H	N	L	VL	DK

10. How much potential do each of the following drugs have to cause **proarrhythmia in patients with sustained VT and poor left ventricular function:** (Circle one response for **each** drug)

	Very High	High	Neither High Nor Low	Low	Very Low	Don't Know
a. Amiodarone?	VH	H	N	L	VL	DK
b. Beta-Blockers?	VH	H	N	L	VL	DK
c. Disopyramide?	VH	H	N	L	VL	DK
d. Encainide?	VH	H	N	L	VL	DK
e. Flecainide?	VH	H	N	L	VL	DK
f. Mexiletine?	VH	H	N	L	VL	DK
g. Procainamide?	VH	H	N	L	VL	DK
h. Quinidine?	VH	H	N	L	VL	DK
i. Tocainide?	VH	H	N	L	VL	DK

11. How much potential do each of the following drugs have to cause **negative inotropic effects:** (Circle one response for **each** drug)

	Very High	High	Neither High Nor Low	Low	Very Low	Don't Know
a. Amiodarone?	VH	H	N	L	VL	DK
b. Beta-Blockers?	VH	H	N	L	VL	DK
c. Disopyramide?	VH	H	N	L	VL	DK
d. Encainide?	VH	H	N	L	VL	DK
e. Flecainide?	VH	H	N	L	VL	DK
f. Mexiletine?	VH	H	N	L	VL	DK
g. Procainamide?	VH	H	N	L	VL	DK
h. Quinidine?	VH	H	N	L	VL	DK
i. Tocainide?	VH	H	N	L	VL	DK

12. Under what conditions would you consider using the following drugs to **initiate** treatment of patients with **symptomatic ventricular arrhythmia and CHD but no sustained VT:** (Check one response for **each** drug)

	Inpatient Only	Either Outpatient or Inpatient	Don't Use This Drug
a. Amiodarone?	☐	☐	☐
b. Beta-Blockers?	☐	☐	☐
c. Disopyramide?	☐	☐	☐
d. Encainide?	☐	☐	☐
e. Flecainide?	☐	☐	☐
f. Mexiletine?	☐	☐	☐
g. Procainamide?	☐	☐	☐
h. Quinidine?	☐	☐	☐
i. Tocainide?	☐	☐	☐

13. How often would you obtain electrophysiologic studies for patients with: (Circle one response for **each** patient type)

	Always	Sometimes	Never
a. Asymptomatic ventricular arrhythmia in a patient with no heart disease?	A	S	N
b. Symptomatic ventricular arrhythmia in a patient with no heart disease?	A	S	N
c. Frequent VPCs with episodes of unsustained VT but no CHF in CAD patients?	A	S	N
d. Frequent VPCs and episodes of unsustained VT with CHF?	A	S	N
e. Documented sustained ventricular tachycardia?	A	S	N

14. Which of the following best describes your practice? (Check **one**)

a. _____ Office-based
b. _____ Hospital-based
c. _____ Academic

15. Would you like to receive a printed summary of the results from this survey?

a. _____ Yes
b. _____ No

Please return to:

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THANK YOU!

Effect of Basic Drive Cycle Length on the Yield of Ventricular Tachycardia During Programmed Ventricular Stimulation

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The yield of sustained, monomorphic ventricular tachycardia (VT) induced by programmed ventricular stimulation was compared, using basic drive trains of 400 ms, 600 ms and sinus rhythm, to identify the most efficient sequence of basic drive trains to use during programmed stimulation. Fifty-five patients with coronary artery disease and inducible sustained monomorphic VT not requiring countershock to terminate underwent 81 electrophysiology tests in which 1 to 3 extrastimuli were introduced during sinus rhythm and after basic drive trains of 600 and 400 ms. In 72 electrophysiology tests, sustained, monomorphic VT was induced at the right ventricular apex. The yield of VT using a drive cycle length of 400 ms was 63 of 72 (88%), compared to 46 of 72 (64%) when the drive cycle length was 600 ms, and 23 of 72 (32%) when the extrastimuli were introduced during sinus rhythm ($p < 0.001$ for all pairwise comparisons). In 14 electrophysiology tests in which VT was not induced using a 400 ms basic drive cycle length at the apex, the yield of VT was higher using a 400 ms drive cycle length at a second right ventricular site (12 of 14) than with a 600 ms drive cycle length (3 of 12) or sinus rhythm (4 of 12) at the apex ($p < 0.05$). The yield of sustained, monomorphic VT induced by 1 to 3 extrastimuli increases as the basic drive cycle length shortens. Whereas programmed stimulation is conventionally started during sinus rhythm or with a drive cycle length of 600 ms, the present results suggest that starting with a drive cycle length of 400 ms may be more efficient.

(Am J Cardiol 1990;65:49–52)

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Programmed ventricular stimulation is conventionally performed by introducing extrastimuli during sinus rhythm and after basic drive trains of 400 to 600 ms.[1–11] When specified, programmed stimulation has been started during sinus rhythm or with a 600 ms basic drive cycle length.[1–11] However, a prior study demonstrated that the yield of ventricular tachycardia (VT) induced by a single extrastimulus increases as the basic drive cycle length is shortened,[12] suggesting that it may be more efficient to begin programmed stimulation using the shortest instead of the longest basic drive cycle length. To date, no studies have compared the yield of monomorphic VT induced by 1 to 3 extrastimuli using basic drive trains of 400 ms, 600 ms and sinus rhythm. To identify the most efficient sequence of basic drive trains to use during programmed ventricular stimulation, we compared the yield of sustained, monomorphic VT induced by programmed stimulation using basic drive trains of 400 ms, 600 ms and sinus rhythm.

METHODS

Patient characteristics: Our subjects were 55 patients with coronary artery disease and a history of sustained, monomorphic VT who had sustained monomorphic VT inducible by programmed ventricular stimulation and in whom the induced VT could be terminated by pacing. There were 47 men and 8 women, and the mean age was 63 ± 10 years (± standard deviation).

The study protocol was attempted in 145 electrophysiology tests; however, 64 cases were excluded because either sustained VT was not inducible (31), sustained, monomorphic VT requiring countershock to terminate was induced (29) or ventricular fibrillation or polymorphic VT requiring countershock to terminate was induced (4). The results of 81 electrophysiology tests were appropriate for analysis. Thirteen of the 81 electrophysiology tests were performed in the drug-free state, whereas 68 were performed in the presence of ≥1 class I antiarrhythmic drug (36), amiodarone (23) or amiodarone plus a class I drug (9).

Study protocol: Electrophysiology tests were performed in the fasting, nonsedated state after written, informed consent was obtained. Two quadripolar electrode catheters were positioned in the right ventricular apex and right ventricular outflow tract via a femoral vein. Additional electrode catheters were positioned in the high right atrium and His bundle position as clini-

TABLE I Sum of the Extrastimulus Coupling Intervals That Induced VT

Basic Drive Cycle Length*	No. of Extrastimuli That Induced VT		
	1	2	3
400 ms	297 ± 27	559 ± 66	768 ± 71
600 ms	300 ± 33	569 ± 74	782 ± 66
Sinus rhythm	290 ± 14	647 ± 85	835 ± 143
P value	>0.05	>0.05	>0.05

* Mean ± standard deviation (ms).
VT = ventricular tachycardia.

cally indicated. Electrocardiographic leads V_1, I and III and the intracardiac electrograms were recorded with a Siemens-Elema Mingograf-7 recorder. A programmable stimulator (Bloom Associates) was used for pacing. Pacing stimuli were 2 ms in duration and twice diastolic threshold.

Programmed stimulation was started at the right ventricular apex with 1, 2 and 3 extrastimuli using 8-beat basic drive trains at a cycle length of 400 ms. The technique used to scan diastole with the extrastimuli has been described previously.[9] To avoid the induction of nonclinical arrhythmias, coupling intervals were limited to 200 ms.[9] In all patients, the pacing protocol was then repeated using a drive cycle length of 600 ms and then during sinus rhythm. During sinus rhythm, the extrastimuli were introduced after every eighth sinus beat. The endpoint of stimulation at each basic drive cycle length was 1 induction of sustained, monomorphic VT or completion of stimulation with 1, 2 and 3 extrastimuli. If sustained, monomorphic VT was not induced using a drive cycle length of 400 ms at the right ventricular apex, the pacing protocol was repeated at the right ventricular outflow tract or septum in the same sequence used at the apex. Sustained VT was defined as VT lasting ≥30 seconds or requiring termination because of hemodynamic compromise. In accord with the selection criteria for subjects, sustained monomorphic VT was inducible in all subjects using this pacing protocol.

Data analysis: A weighted least squares analysis of categorical data using linear models was used to compare the yield of sustained, monomorphic VT between the basic drive cycle lengths.[13] To compare the percentage of patients at each drive cycle length requiring 3 extrastimuli to induce VT, maximum likelihood contingency table analysis was used.[14] Analysis of variance was used to compare the sum of the coupling intervals that induced VT between the different drive cycle lengths. A p value <0.05 was considered statistically significant.

RESULTS

Effect of the drive cycle length on yield of induced ventricular tachycardia: In 72 electrophysiology tests, sustained, monomorphic VT was induced by programmed stimulation at the right ventricular apex. The yield of VT using a drive cycle length of 400 ms was 63 of 72 (88%), compared to 46 of 72 (64%) when the drive cycle length was 600 ms, and 23 of 72 (32%) when the extrastimuli were introduced during sinus rhythm (mean sinus cycle length 840 ± 154 ms; p <0.001 for all pairwise comparisons).

In 28 of the 72 electrophysiology tests, VT was inducible by programmed stimulation using only 1 of the drive cycle lengths. Among these 28 cases, significantly more were inducible only with a drive cycle length of 400 ms (21 of 28) than with a drive cycle length of 600 ms (4 of 28, p <0.001) or during sinus rhythm (3 of 28, p <0.001).

In 44 of the 72 electrophysiology tests, sustained, monomorphic VT was induced using >1 drive cycle length. In 28 of these 44 tests (64%), the VT induced with the different drive cycle lengths had the same configuration; in 16 cases, the monomorphic VTs induced with the different drive cycle lengths had different configurations.

There was no significant difference in the number of episodes of VT requiring 3 extrastimuli to induce with the 400 ms drive cycle length (35%) compared with the 600 ms drive cycle length (41%). However, a greater percentage of episodes of VT induced during sinus rhythm (74%) required 3 extrastimuli to induce as compared to when the drive cycle length was 400 or 600 ms (p <0.01).

Comparison of coupling intervals that induced ventricular tachycardia: To determine whether the different yields of induced VT with the various drive cycle lengths was attributable to a difference in the coupling intervals used to induce VT, the sums of the coupling intervals used to induce VT with 1, 2 or 3 extrastimuli were compared (Table I). There were no significant differences between the 400 or 600 ms drive cycle lengths or sinus rhythm.

Yield of ventricular tachycardia at the second right ventricular site: In only 18 of the 81 electrophysiology tests was sustained, monomorphic VT not inducible using a drive cycle length of 400 ms at the right ventricular apex. In 14 of these tests, the pacing protocol was completed both at the right ventricular apex and at the right ventricular outflow tract or septum with a drive cycle length of 400 ms. The yield of sustained monomorphic VT was significantly higher with a 400-ms drive cycle length at the second right ventricular site (12 of 14) than with a 600-ms drive cycle length (3 of 12) or sinus rhythm (4 of 12) at the apex (p <0.05).

Cycle length of induced ventricular tachycardia: There were no significant differences among the mean cycle lengths of the VTs induced using a drive cycle length of 400 ms (377 ± 78 ms), 600 ms (381 ± 80 ms) or sinus rhythm (402 ± 82 ms).

Yield of nonclinical arrhythmias: Four electrophysiology tests were excluded from this study because sustained polymorphic VT or ventricular fibrillation was induced. One of these nonclinical arrhythmias was induced by 1 extrastimulus, 2 were induced by 2 extrastimuli and 1 by 3 extrastimuli. All were induced using

a drive cycle length of 400 ms, which was the first drive cycle length used.

DISCUSSION

Major findings: In our study, basic drive cycle lengths of 400 ms, 600 ms and sinus rhythm were compared because these are the drive cycle lengths that are conventionally used during clinical electrophysiology tests. The results of our study demonstrate that there is a significant increase in the yield of sustained, monomorphic VT as the basic drive cycle length is shortened. By starting programmed stimulation using a drive cycle length of 400 ms, sustained monomorphic VT was induced in 88% of patients with VT inducible at the right ventricular apex with 1 to 3 extrastimuli. In contrast, using a drive cycle length of 600 ms or sinus rhythm, the yield of sustained, monomorphic VT was only 64 and 32%, respectively. When VT was not induced using a drive cycle length of 400 ms at the right ventricular apex, the yield of sustained, monomorphic VT was substantially higher using a drive cycle length of 400 ms at a second right ventricular site compared to continuing with programmed stimulation at the right ventricular apex using a drive cycle length of 600 ms or sinus rhythm.

Whereas programmed ventricular stimulation is conventionally started during sinus rhythm or with a drive cycle length of 600 ms,[1–11] our results suggest that it may be more efficient to start with a drive cycle length of 400 ms. This is particularly relevant to patients who are undergoing an electrophysiology test for the purpose of evaluating antiarrhythmic drug efficacy. In these patients, the first induced episode of sustained, monomorphic VT may be sufficient to demonstrate drug inefficacy and may serve as an adequate endpoint for stimulation. If VT is not induced by programmed stimulation with 1 to 3 extrastimuli at the right ventricular apex, it would be more efficient to repeat programmed stimulation with 1 to 3 extrastimuli at a second right ventricular site instead of using longer basic drive cycle lengths at the apex.

Possible mechanisms: Because the ventricular effective refractory period decreases as the basic drive cycle length is shortened,[15] a possible mechanism accounting for the higher yield of sustained, monomorphic VT with the use of a 400-ms drive cycle length is that shorter extrastimulus coupling intervals were achieved than with the use of a 600-ms drive cycle length or during sinus rhythm. However, no significant difference in the sum of the coupling intervals that induced VT was found among the episodes of VT induced with the same number of extrastimuli using a drive cycle length of 400 ms, 600 ms or sinus rhythm. This suggests that the higher yield of VT with the 400-ms drive cycle length is not attributable to the use of shorter extrastimulus coupling intervals. Similarly, prior studies also have found that the facilitation of VT induction at shorter drive cycle lengths is not explained solely by achievement of shorter coupling intervals.[12,16]

The basic drive is likely to influence the electrophysiologic properties of the VT reentry circuit and of the surrounding myocardium, and therefore it is possible that the yield of VT was highest with the 400-ms drive cycle length because of a direct effect of the shorter drive cycle length on refractoriness, conduction within the reentry circuit, intervening myocardium or a combination.[17]

Specificity of programmed stimulation: The use of 3 extrastimuli has been demonstrated to increase the sensitivity of programmed ventricular stimulation compared to the use of 1 or 2 extrastimuli.[3–5] On the other hand, the use of 3 extrastimuli may also impair the specificity of programmed stimulation by resulting in the induction of nonclinical forms of polymorphic VT and ventricular fibrillation.[4,5] However, with limitation of the extrastimulus coupling intervals to 200 ms, sustained polymorphic VT or ventricular fibrillation was induced in only 4 of the 145 electrophysiology tests in which the study protocol was attempted. Therefore, our results demonstrate that the early use of 3 extrastimuli in a stimulation protocol need not necessarily impair the specificity of programmed ventricular stimulation.

Limitations: Because our study design required multiple attempts at the induction of VT, only patients who had VT that could be terminated with pacing were included. Therefore, our results may not apply to patients who have hemodynamically unstable VT or VT requiring countershock to terminate.

A second possible limitation is that a high percentage of the patients (84%) were being treated with antiarrhythmic drugs at the time of electrophysiologic testing. The possibility that the antiarrhythmic drugs influenced the relative yield of VT with the various basic drive cycle lengths tested cannot be ruled out.

Acknowledgment: We are grateful to Deanne Backhaus for secretarial assistance.

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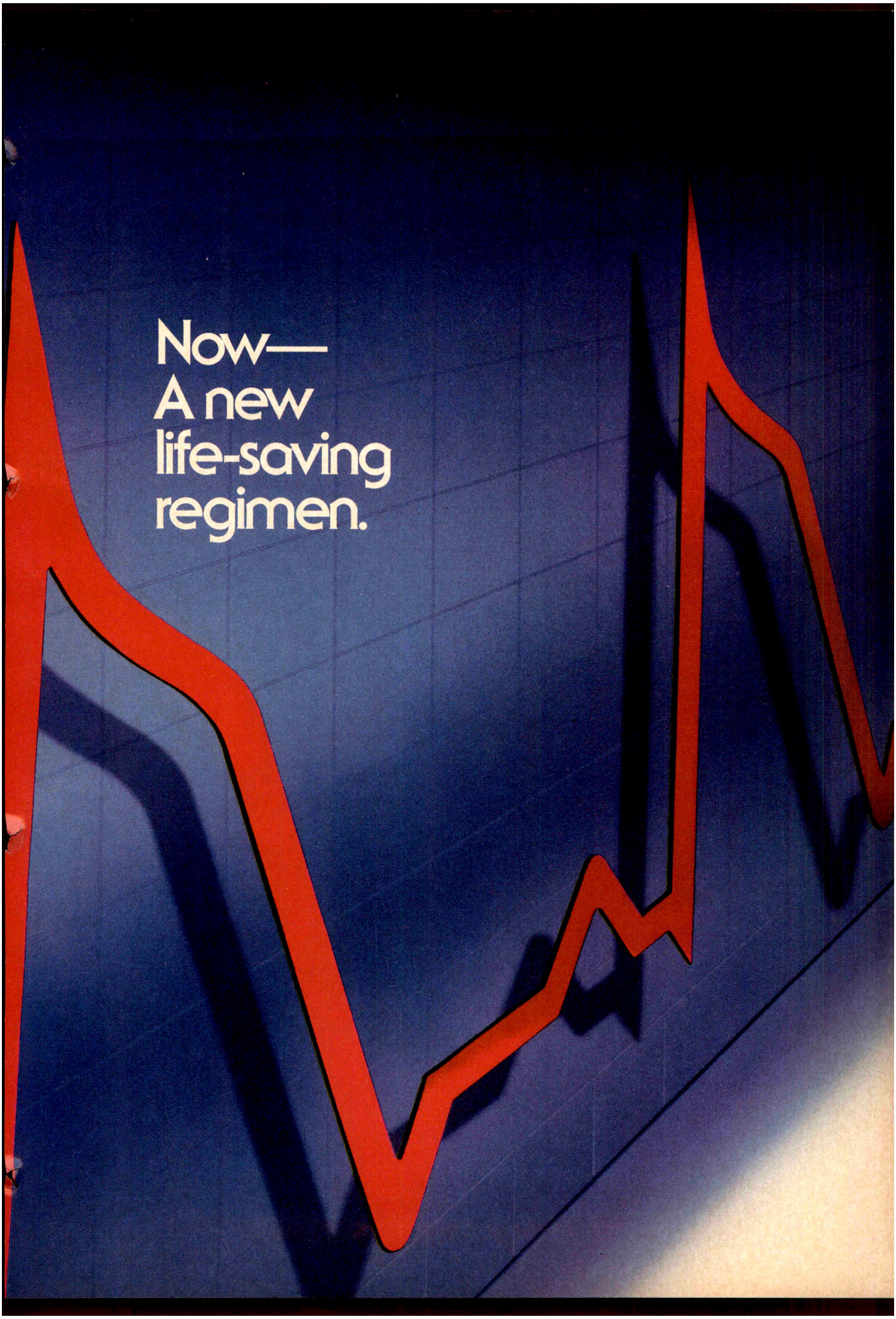
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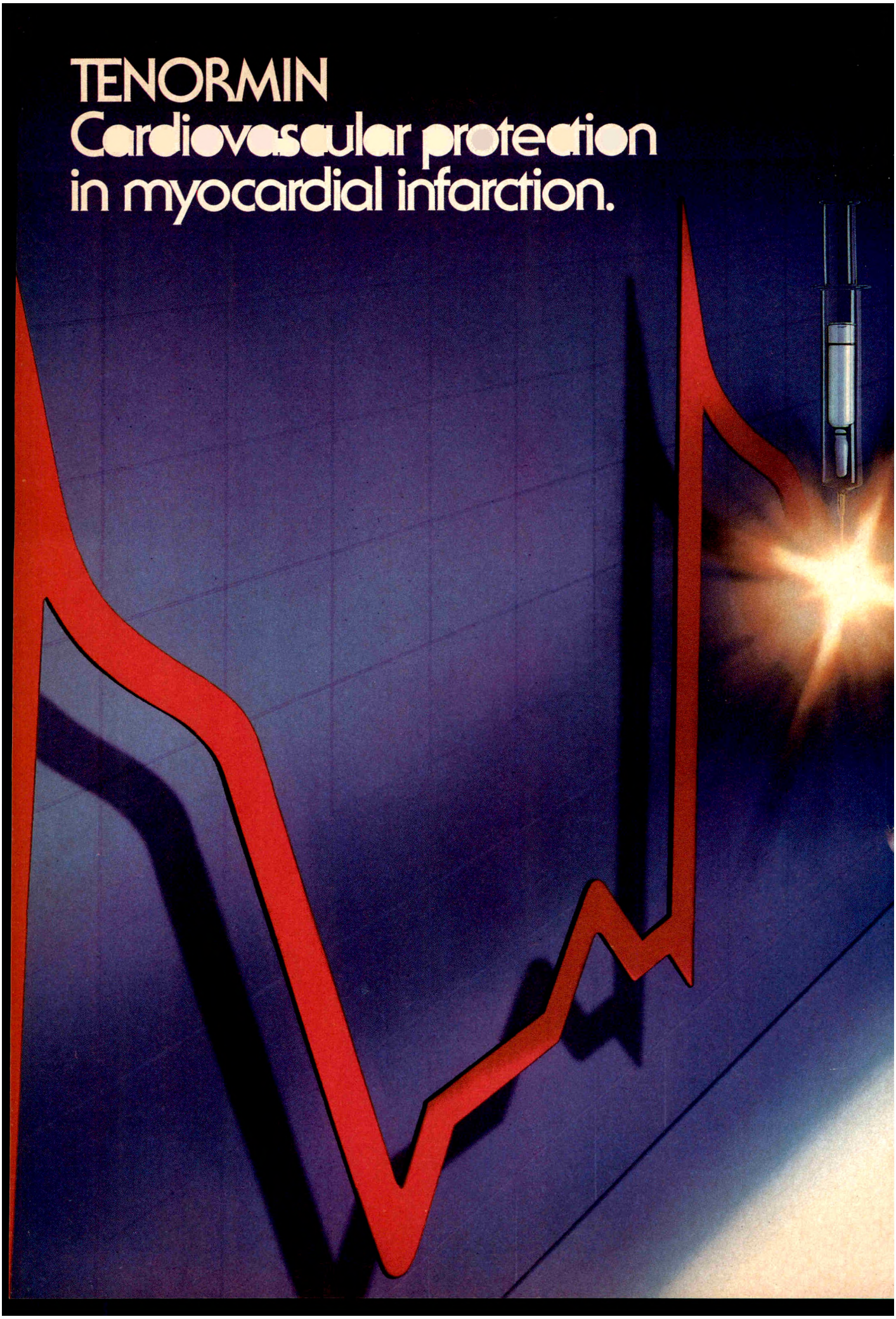
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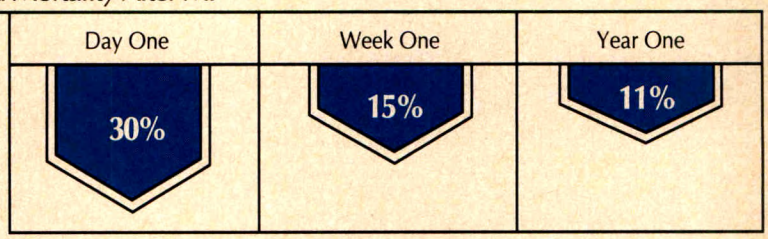
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In the ISIS-1 trial—"Randomised Trial of Intravenous Atenolol Among 16,027 Cases of Suspected Acute Myocardial Infarction"— in patients randomized within 12 hours of symptom onset, the TENORMIN Regimen reduced MI mortality by 30% at day one and maintained a significant reduction throughout a year of follow-up. When patients were randomized within 2 hours of the onset of pain, first-week mortality was reduced by 53%.[1]

*Significantly Reduced Mortality After MI**



*Adapted from ISIS-1 study.[1]

†Data derived.

	Day One	Week One	Year One
Control-group deaths	171/7,990	365/7,990	923/7,930
TENORMIN-group deaths	121/8,037	313/8,037	825/7,968
	$2P < .003$†	$2P < .04$	$2P < .01$

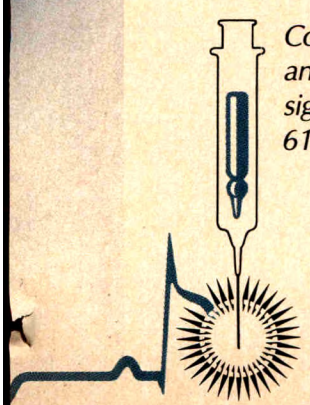
Good clinical judgment suggests that patients who are dependent on sympathetic stimulation for adequate cardiac output and BP are not good candidates for beta blockade. In addition to patients excluded from the ISIS-1 study, those with borderline BP (ie, systolic < 120, especially if over age 60) are less likely to benefit.

Provides cardiovascular protection...

A second major study—"Reduction of Infarct Size, Arrhythmias and Chest Pain by Early Intravenous Beta Blockade in Suspected Acute Myocardial Infarction"— showed that the TENORMIN Regimen reduced enzyme elevation and sudden death while also reducing chest pain and frequency of ventricular premature beats.[2]

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Compared to controls, patients on the TENORMIN Regimen had less need for antifailure, antiarrhythmic, and antianginal therapy.[2] *In fact, TENORMIN reduced signs of heart failure and cardiogenic shock, and it reduced R-on-T ectopies by 61% (2P < .0001).*[2]



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INDICATIONS AND USAGE: Hypertension: TENORMIN is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-type diuretic.

Angina Pectoris Due to Coronary Atherosclerosis: TENORMIN is indicated for the long-term management of patients with angina pectoris.

Acute Myocardial Infarction: TENORMIN is indicated in the management of hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality. Treatment can be initiated as soon as the patient's clinical condition allows. (See DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS.) In general, there is no basis for treating patients like those who were excluded from the ISIS-1 trial (blood pressure less than 100 mm Hg systolic, heart rate less than 50 bpm) or have other reasons to avoid beta blockade. As noted above, some subgroups (eg, elderly patients with systolic blood pressure below 120 mm Hg) seemed less likely to benefit.

CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure. (See WARNINGS.)

WARNINGS: Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, TENORMIN should be administered cautiously. Both digitalis and atenolol slow AV conduction.

In patients with acute myocardial infarction, cardiac failure which is not promptly and effectively controlled by 80 mg of intravenous furosemide or equivalent therapy is a contraindication to beta-blocker treatment.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic and the response observed closely. If cardiac failure continues despite adequate digitalization and diuresis, TENORMIN should be withdrawn. (See DOSAGE AND ADMINISTRATION.)

Cessation of Therapy With TENORMIN: Patients with coronary artery disease, who are being treated with TENORMIN, should be advised against abrupt discontinuation of therapy. Severe exacerbation of angina and the occurrence of myocardial infarction and ventricular arrhythmias have been reported in angina patients following the abrupt discontinuation of therapy with other beta blockers. The last two complications may occur with or without preceding exacerbation of the angina pectoris. To date, there has been no report of myocardial infarction or severe angina upon withdrawal of TENORMIN, probably due to its long plasma half-life. Because of the problems encountered with other beta blockers, when discontinuation of TENORMIN is planned, the patients should be carefully observed and advised to limit physical activity to a minimum. If the angina worsens or acute coronary insufficiency develops, it is recommended that TENORMIN be promptly reinstituted, at least temporarily. (See DOSAGE AND ADMINISTRATION.)

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, TENORMIN may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, the lowest possible dose of TENORMIN should be used with therapy initiated at 50 mg and a beta$_2$-stimulating agent (bronchodilator) should be made available. If dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels.

Anesthesia and Major Surgery: As with all beta-receptor blocking drugs it may be decided to withdraw TENORMIN before surgery. In this case 48 hours should be allowed to elapse between the last dose and anesthesia. If treatment is continued, care should be taken when using anesthetic agents which depress the myocardium such as ether, cyclopropane, and trichloroethylene.

Additionally, caution should be used when TENORMIN I.V. Injection is administered concomitantly with such agents.

TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents: eg, dobutamine or isoproterenol with caution (see section on OVERDOSAGE). Manifestations of excessive vagal tone (eg, profound bradycardia, hypotension) may be corrected with atropine (1-2 mg IV).

Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism. Patients suspected of having thyroid disease should be monitored closely when administering TENORMIN I.V. Injection. Abrupt withdrawal of beta blockade might precipitate a thyroid storm; therefore, patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely. (See DOSAGE AND ADMINISTRATION.)

PRECAUTIONS: General: Patients already on a beta blocker must be evaluated carefully before TENORMIN is administered. Initial and subsequent TENORMIN dosages can be adjusted downward depending on clinical observations including pulse and blood pressure.

Impaired Renal Function: The drug should be used with caution in patients with impaired renal function. (See DOSAGE AND ADMINISTRATION.)

Drug Interactions: Catecholamine-depleting drugs (eg, reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with TENORMIN plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Should it be decided to discontinue therapy in patients receiving beta blockers and clonidine concurrently, the beta blocker should be discontinued several days before the gradual withdrawal of clonidine.

Caution should be exercised with TENORMIN I.V. Injection when given in close proximity with drugs that may also have a depressant effect on myocardial contractility. On rare occasions, concomitant use of intravenous beta blockers and intravenous verapamil has resulted in serious adverse reactions, especially in patients with severe cardiomyopathy, congestive heart failure, or recent myocardial infarction.

Information on concurrent usage of atenolol and aspirin is limited. Data from several studies, ie, TIMI-II, ISIS-2, currently do not suggest any clinical interaction between aspirin and beta blockers in the acute myocardial infarction setting.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing oral dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human antihypertensive dose,* did not indicate a carcinogenic potential in rodents. Results of various mutagenicity studies support this finding.

Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human antihypertensive dose*) was unaffected by atenolol administration.

Animal Toxicology: Chronic studies employing oral atenolol performed in animals have revealed the occurrence of vacuolation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels of atenolol (starting at 15 mg/kg/day or 7.5 times the maximum recommended human antihypertensive dose*) and increased incidence of atrial degeneration of hearts of male rats at 300 but not 150 mg atenolol/kg/day (150 and 75 times the maximum recommended human antihypertensive dose,* respectively).

Usage in Pregnancy: Pregnancy Category C: Atenolol has been shown to produce a dose-related increase in embryo/fetal resorptions in rats at doses equal to or greater than 50 mg/kg/day or 25 or more times the maximum recommended human antihypertensive dose.* Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg/day or 12.5 times the maximum recommended human antihypertensive dose.* There are no adequate and well-controlled studies in pregnant women. TENORMIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

* Based on a 50 kg patient weight.

Nursing Mothers: Atenolol is excreted in human breast milk at a ratio of 1.5 to 6.8 when compared to the concentration in plasma. Caution should be exercised when TENORMIN is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient. Frequency estimates were derived from controlled studies in hypertensive patients in which adverse reactions were either volunteered by the patient (US studies) or elicited, eg, by checklist (foreign studies). The reported frequency of elicited adverse effects was higher for both TENORMIN and placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects of TENORMIN and placebo is similar, causal relationship to TENORMIN is uncertain.

The following adverse-reaction data present frequency estimates in terms of percentages: first from the US studies (volunteered side effects) and then from both US and foreign studies (volunteered and elicited side effects):

US STUDIES (ATENOLOL, n≈164; PLACEBO, n≈206) (% ATENOLOL-% PLACEBO):

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (0%-0.5%), postural hypotension (2%-1%), leg pain (0%-0.5%)

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (4%-1%), vertigo (2%-0.5%), light-headedness (1%-0%), tiredness (0.6%-0.5%), fatigue (3%-1%), lethargy (1%-0%), drowsiness (0.6%-0%), depression (0.6%-0.5%), dreaming (0%-0%)

GASTROINTESTINAL: diarrhea (2%-0%), nausea (4%-1%)

RESPIRATORY (see WARNINGS): wheeziness (0%-0%), dyspnea (0.6%-1%)

TOTALS US AND FOREIGN STUDIES (ATENOLOL, n≈399; PLACEBO, n≈407):

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (12%-5%), postural hypotension (4%-5%), leg pain (3%-1%)

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (13%-6%), vertigo (2%-0.2%), light-headedness (3%-0.7%), tiredness (26%-13%), fatigue (6%-5%), lethargy (3%-0.7%), drowsiness (2%-0.5%), depression (12%-9%), dreaming (3%-1%)

GASTROINTESTINAL: diarrhea (3%-2%), nausea (3%-1%)

RESPIRATORY (see WARNINGS): wheeziness (3%-3%), dyspnea (6%-4%)

In a series of investigations in the treatment of acute myocardial infarction, bradycardia and hypotension occurred more commonly, as expected for any beta blocker, in atenolol-treated patients than in control patients. However, these usually responded to atropine and/or to withholding further dosage of atenolol. The incidence of heart failure was not increased by atenolol. Inotropic agents were infrequently used. The reported frequency of these and other events occurring during these investigations is given below.

In a study of 477 patients, the following adverse events were reported during either intravenous and/or oral atenolol administration:

CONVENTIONAL THERAPY PLUS ATENOLOL (n≈244): bradycardia, 43 (18%); hypotension, 60 (25%); bronchospasm, 3 (1.2%); heart failure, 46 (19%); heart block, 11 (4.5%); BBB + major axis deviation, 16 (6.6%); supraventricular tachycardia, 28 (11.5%); atrial fibrillation, 12 (5%); atrial flutter, 4 (1.6%); ventricular tachycardia, 39 (16%); cardiac reinfarction, 0 (0%); total cardiac arrests, 4 (1.6%); nonfatal cardiac arrests, 4 (1.6%); deaths, 7 (2.9%); cardiogenic shock, 1 (0.4%); development of ventricular septal defect, 0 (0%); development of mitral regurgitation, 0 (0%); renal failure, 1 (0.4%); pulmonary emboli, 3 (1.2%)

CONVENTIONAL THERAPY ALONE (n≈233): bradycardia, 24 (10%); hypotension, 34 (15%); bronchospasm, 2 (0.9%); heart failure, 56 (24%); heart block, 10 (4.3%); BBB + major axis deviation, 28 (12%); supraventricular tachycardia, 45 (19%); atrial fibrillation, 29 (11%); atrial flutter, 7 (3%); ventricular tachycardia, 52 (22%); cardiac reinfarction, 6 (2.6%); total cardiac arrests, 16 (6.9%); nonfatal cardiac arrests, 12 (5.1%); deaths, 16 (6.9%); cardiogenic shock, 4 (1.7%); development of ventricular septal defect, 2 (0.9%); development of mitral regurgitation, 2 (0.9%); renal failure, 0 (0%); pulmonary emboli, 0 (0%)

In the subsequent International Study of Infarct Survival (ISIS-1) including over 16,000 patients of whom 8,037 were randomized to receive TENORMIN(atenolol) treatment, the dosage of intravenous and subsequent oral TENORMIN was either discontinued or reduced for the following reasons:

REASONS FOR REDUCED DOSAGE

IV ATENOLOL* REDUCED DOSE (< 5 mg): hypotension/bradycardia, 105 (1.3%); cardiogenic shock, 4 (.04%); reinfarction, 0 (0%); cardiac arrest, 5 (.06%); heart block (> first degree), 5 (.06%); cardiac failure, 1 (.01%); arrhythmias, 3 (.04%); bronchospasm, 1 (.01%)

ORAL PARTIAL DOSE: hypotension/bradycardia, 1168 (14.5%); cardiogenic shock, 35 (.44%); reinfarction, 5 (.06%); cardiac arrest, 28 (.34%); heart block (> first degree), 143 (1.7%); cardiac failure, 233 (2.9%); arrhythmias, 22 (.27%); bronchospasm, 50 (.62%)

* Full dosage was 10 mg and some patients received less than 10 mg but more than 5 mg.

POTENTIAL ADVERSE EFFECTS: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects of TENORMIN.

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Fever, combined with aching and sore throat, laryngospasm, and respiratory distress.

Central Nervous System: Reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation of time and place; short-term memory loss; emotional lability with slightly clouded sensorium; and, decreased performance on neuropsychometrics.

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Other: Reversible alopecia, Peyronie's disease, erythematous rash, Raynaud's phenomenon.

Miscellaneous: There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small, and in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy. (See DOSAGE AND ADMINISTRATION.)

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with TENORMIN during investigational use and foreign marketing experience. Furthermore, a number of patients who had previously demonstrated established practolol reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the reaction.

OVERDOSAGE: To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. The most common effects expected with overdosage of a beta-adrenergic blocking agent are bradycardia, congestive heart failure, hypotension, bronchospasm, and hypoglycemia.

In the case of overdosage, treatment with TENORMIN should be stopped and the patient carefully observed. TENORMIN can be removed from the general circulation by hemodialysis. In addition to gastric lavage, the following therapeutic measures are suggested if warranted:

BRADYCARDIA: Atropine or another anticholinergic drug.

HEART BLOCK (SECOND OR THIRD DEGREE): Isoproterenol or transvenous cardiac pacemaker.

CONGESTIVE HEART FAILURE: Conventional therapy.

HYPOTENSION (DEPENDING ON ASSOCIATED FACTORS): Epinephrine rather than isoproterenol or norepinephrine may be useful in addition to atropine and digitalis.

BRONCHOSPASM: Aminophylline, isoproterenol, or atropine.

HYPOGLYCEMIA: Intravenous glucose.

DOSAGE AND ADMINISTRATION: Hypertension: The initial dose of TENORMIN is 50 mg given as one tablet a day either alone or added to diuretic therapy. The full effect of this dose will usually be seen within one to two weeks. If an optimal response is not achieved, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Increasing the dosage beyond 100 mg a day is unlikely to produce any further benefit.

TENORMIN may be used alone or concomitantly with other antihypertensive agents including thiazide-type diuretics, hydralazine, prazosin, and alpha-methyldopa.

Angina Pectoris: The initial dose of TENORMIN is 50 mg given as one tablet a day. If an optimal response is not achieved within one week, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Some patients may require a dosage of 200 mg once a day for optimal effect.

Twenty-four hour control with once daily dosing is achieved by giving doses larger than necessary to achieve an immediate maximum effect. The maximum early effect on exercise tolerance occurs with doses of 50 to 100 mg, but at these doses the effect at 24 hours is attenuated, averaging about 50% to 75% of that observed with once a day oral doses of 200 mg.

Acute Myocardial Infarction: In patients with definite or suspected acute myocardial infarction, treatment with TENORMIN I.V. Injection should be initiated as soon as possible after the patient's arrival in the hospital and after eligibility is established. Such treatment should be initiated in a coronary care or similar unit immediately after the patient's hemodynamic condition has stabilized. Treatment should begin with the intravenous administration of 5 mg TENORMIN over 5 minutes followed by another 5 mg intravenous injection 10 minutes later. TENORMIN I.V. Injection should be administered under carefully controlled conditions including monitoring of blood pressure, heart rate, and electrocardiogram. Dilutions of TENORMIN I.V. injection in Dextrose Injection USP, Sodium Chloride Injection USP, or Sodium Chloride and Dextrose Injection may be used. These admixtures are stable for 48 hours if they are not used immediately.

In patients who tolerate the full intravenous dose (10 mg), TENORMIN Tablets 50 mg should be initiated 10 minutes after the last intravenous dose followed by another 50 mg oral dose 12 hours later. Thereafter, TENORMIN can be given orally either 100 mg once daily or 50 mg twice a day for a further 6-9 days or until discharge from the hospital. If bradycardia or hypotension requiring treatment or any other untoward effects occur, TENORMIN should be discontinued. (See full prescribing information prior to initiating therapy with TENORMIN Tablets.)

Data from other beta blocker trials suggest that if there is any question concerning the use of IV beta blocker or clinical estimate that there is a contraindication, the IV beta blocker may be eliminated and patients fulfilling the safety criteria may be given TENORMIN Tablets 50 mg twice daily or 100 mg once a day for at least seven days (if the IV dosing is excluded).

Although the demonstration of efficacy of TENORMIN is based entirely on data from the first seven postinfarction days, data from other beta blocker trials suggest that treatment with beta blockers that are effective in the postinfarction setting may be continued for one to three years if there are no contraindications.

TENORMIN is an additional treatment to standard coronary care unit therapy.

Patients With Renal Impairment: Since TENORMIN is excreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of TENORMIN occurs until creatinine clearance falls below 35 mL/min/1.73 m^2 (normal range is 100-150 mL/min/1.73 m^2); therefore, the following maximum oral dosages are recommended for patients with renal impairment.

Creatinine Clearance (mL/min/1.73 m^2)	Atenolol Elimination Half-Life (h)	Maximum Dosage
15-35	16-27	50 mg daily
<15	>27	50 mg every other day

Patients on hemodialysis should be given 50 mg after each dialysis; this should be done under hospital supervision as marked falls in blood pressure can occur.

Cessation of Therapy in Patients With Angina Pectoris: If withdrawal of TENORMIN therapy is planned, it should be achieved gradually, and patients should be carefully observed and advised to limit physical activity to a minimum.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Rev H 8/

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New Insights into Pacemaker Syndrome Gained from Hemodynamic, Humoral and Vascular Responses During Ventriculo-Atrial Pacing

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Ventricular pacing is performed during programmed electrical stimulation and during normal functioning of single chamber (VVI or VVIR) pacemakers. In many patients, retrograde ventriculo-atrial (V-A) conduction may occur and evoke hemodynamic and reflex neurohumoral responses, which are unique to this pacing mode. Accordingly, forearm blood flow, forearm vascular resistance, mean and phasic arterial pressure, cardiac output and plasma norepinephrine, epinephrine and dopamine were measured during atrial, ventricular and V-A pacing at a cycle length of 600 ms (100 beats/min) before and after regional α blockade with intraarterial phentolamine in 16 patients with a left ventricular ejection fraction >35% and little or no symptoms of congestive heart failure. During V-A pacing, cardiac output decreased by 10%, whereas forearm vascular resistance increased from 52 ± 7 to 70 ± 9 U ($p < 0.001$) and plasma norepinephrine increased from 183 ± 27 to 232 ± 27 pg/ml ($p < 0.01$). Phentolamine nearly abolished the increase in forearm vascular resistance in response to V-A pacing (18 ± 4.1 U before vs 5.8 ± 1.5 U after, $p < 0.05$). The change in forearm vascular resistance with V-A pacing correlated with systolic arterial pressure, but not with changes in mean arterial pressure, pulse pressure, cardiac output, mean or peak right atrial pressure, pulmonary artery or pulmonary capillary wedge pressure. These results suggest that forearm vascular resistance responses to V-A pacing are mediated mainly by α-adrenergic receptors, through the arterial baroreflexes. These sympathetic vasoconstrictor and humoral responses may be important in compensating for hemodynamic abnormalities during ventricular arrhythmias, and inadequate sympathetic responses may play a role in the genesis of pacemaker syndrome.

(Am J Cardiol 1990;65:53–59)

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Programmed electrical stimulation is a widely accepted technique for the evaluation and treatment of patients with ventricular arrhythmias.[1] In some centers, programmed electrical stimulation is performed during ventricular pacing alone, whereas in others it is performed during sinus rhythm as well as with ventricular paced drives.[2,3] In addition, with the advent of rate-responsive pacing, many patients are ventricularly paced at rates of 100 to 150 beats/min.

When the ventricle is paced, retrograde conduction to the atria occurs in many patients.[4,5] The presence of retrograde ventriculo-atrial (V-A) conduction during pacing may be associated with a variety of hemodynamic, neurohumoral and vascular responses. The changes that occur with different pacing modes may alter the autonomic milieu and thus may contribute to arrhythmogenesis.

Previous investigators have studied the effect of V-A conduction on hemodynamics.[6,7] These studies are limited by the absence of information about the humoral and vascular responses to pacing, as well as the inclusion of patients with widely varying degrees of underlying heart disease. Our purpose was to compare the hemodynamic, humoral and forearm vascular responses to ventricular, atrial and V-A pacing at 100 beats/min (600 ms) in patients with relatively preserved ventricular function undergoing electrophysiology study. These responses were studied before and after regional α blockade with intraarterial phentolamine to assess the role of α-adrenergic receptors in the mediation of the vasoconstrictor responses we observed.

METHODS

The study group consisted of 16 consecutive adult patients referred for electrophysiologic study to evaluate symptomatic or suspected cardiac arrhythmias. Patients were excluded from this study if they had an ejection fraction <35% determined by radionuclide angiography or symptoms of New York Heart Association class III or IV congestive heart failure. Patients with diabetes mellitus or inability to cooperate with the measurement of forearm blood flow were excluded from this study. Cardioactive medications (e.g., vasodilators, nitrates, etc.) were held for ≥4 half-lives before the study.

Study protocol: All studies were performed in fasting, nonsedated patients after they gave written informed consent. The protocol was approved by the institutional review board. Two or 3 multipolar catheters were introduced percutaneously through the femoral vein and positioned in the heart in the right atrial ap-

TABLE I Mean Pressure Before and After Intraarterial Phentolamine (mm Hg)

	RA	PA	PCW	MAP
Before phentolamine				
Baseline	3.7 ± 0.5	13.3 ± 1	7.5 ± 0.8	93 ± 1.6
V	6.1 ± 0.5§	16.6 ± 1§	10 ± 0.9‡	91 ± 2.5
A	3.8 ± 0.5	13.2 ± 1	6 ± 0.8*	99 ± 1.5*
V-A	8.0 ± 0.5§	16.6 ± 1§	11.3 ± 1§	94 ± 2
After phentolamine				
Baseline	4.0 ± 0.7	13 ± 1*	6.5 ± 0.9	95 ± 2.0
V	8.0 ± 2 (n = 5)	15.5 ± 1§	10 ± 1‡	91 ± 2.7†
A	5.0 ± 0.9 (n = 5)	13 ± 16	6.5 ± 1	102 ± 2*
V-A	7.2 ± 1 (n = 5)	16 ± 1§	11 ± 1§	90 ± 2.7*

* p <0.01; † p <0.05; ‡ p <0.001; § p <0.0001, vs baseline.
A = atrial pacing; MAP = mean arterial pressure; PA = pulmonary artery; PCW = pulmonary capillary wedge; RA = right atrial; V = ventricular pacing; V-A = ventriculoatrial pacing.

TABLE II Statistical Comparisons of Hemodynamic Variables and Vascular Responses Before and After Phentolamine Between Different Pacing Modes

	V vs V-A	V vs A	V-A vs A
Before phentolamine			
MAP	0.05	0.05	NS
RA	0.01	0.001	0.0001
PA	NS	0.001	0.002
PCW	0.05	0.0001	0.0001
CO	NS	0.01	0.0001
FVR	0.03	NS	0.01
After phentolamine			
MAP	NS	0.01	0.005
RA	—	—	—
PA	NS	0.001	0.0001
PCW	NS	0.001	0.001
CO	—	—	—
FVR	NS	0.06	0.001

A = atrial pacing; CO = cardiac output; FVR = forearm vascular resistance; MAP = mean arterial pressure; NS = not significant; PA = pulmonary artery pressure; PCW = pulmonary capillary wedge pressure; RA = right atrial pressure; V = ventricular pacing; V-A = ventriculoatrial pacing; — = not done.

pendage near the His bundle and in the right ventricular apex. Recordings of phasic and mean right atrial, pulmonary artery and pulmonary capillary wedge pressure were obtained over a 5-minute period using a 7.5Fr Swan-Ganz catheter (Critikon). An 18-gauge Teflon-coated cannula was inserted into the right brachial artery for continuous arterial pressure monitoring. Programmed electrical stimulation was performed with a standard, programmable stimulator and recordings were made with a 16-channel physiologic recorder at a paper speed of 50 to 100 mm/s. On completion of the electrophysiologic study, the pacing research protocol was performed after baseline heart rate and blood pressure were reestablished.

Each patient was paced in each of 3 modes at a cycle length of 600 ms for 5 minutes. A cycle length of 600 ms was selected because it was at least 150 ms greater than each patient's spontaneous sinus cycle length. Patients were excluded if they had frequent premature atrial contractions or premature ventricular contractions (>5 to 10 beats/min), and therefore, atrial and ventricular pacing was essentially overdrive pacing. The third pacing mode was V-A pacing, which was performed by pacing the ventricle at 600 ms with an atrial stimulus coupled to each ventricular stimulus at 100 to 150 ms.

Venous occlusion plethysmography: Forearm blood flow was measured by venous occlusion plethysmography with a mercury-in-silastic strain gauge plethysmograph (EC-3 or EC-4; DE Hokanson). The technique of venous occlusion plethysmography used has been described previously in detail.[8] A minimum of 5 consecutive curves was averaged to obtain a mean value. Forearm blood flow and phasic or mean arterial pressure were recorded on a direct-writing Gould physiologic recorder (2800 S). Forearm vascular resistance was calculated by dividing the mean arterial pressure (diastolic plus one-third of pulse pressure, in mm Hg) by the forearm blood flow (expressed as ml/min/100 ml of forearm volume). Forearm vascular resistance values are expressed as U throughout.

Protocol: Each patient was allowed to rest comfortably in the supine position for 15 minutes. Hemodynamic measurements were obtained and cardiac output was measured with thermodilution by the injection of 10 cc of D_5W in triplicate.

After the determination of baseline forearm blood flow each patient was randomly allocated to a sequence of pacing. Each pacing mode was performed for 5 minutes. The first 1.5 minutes were used to measure forearm blood flow and arterial pressure, as well as right atrial, pulmonary artery and pulmonary capillary wedge pressures. The next 2.5 minutes were used to determine cardiac output. During the final minute, a blood sample (10 cc) was obtained from the right atrium for determination of plasma catecholamine levels. The patient then had a 5-minute rest period during which baseline forearm blood flow and pressure were recorded for 1 minute before initiation of the next pacing mode.

After measurements during all 3 pacing modes were obtained, phentolamine was infused into the brachial artery over 10 minutes with a Harvard infusion pump at 12 μg/100 ml forearm volume/min (maximum 1.5 mg/10 minutes). After a stable baseline was reestablished, repeat measurements were made. Each of the pacing protocols was repeated for 3 minutes, during which forearm blood flow and hemodynamics were measured. A 3-minute recovery period was interposed between each intervention to reestablish baseline.

Blood samples for catecholamines were collected in prechilled heparinized tubes and the plasma was stored at −75°C until assayed. Catecholamines were assayed by a high-performance liquid chromatography with electrochemical detection.[9] Detection in this system is coulometric and the sensitivity is <5 pg/ml.

Statistical analysis: The Shapiro-Wilk normality test was performed on all the data to determine if they were normally distributed. For normally distributed data, parametric tests were used. Paired *t* tests were used to test for significant change from a measurement's baseline, with each pacing mode. For data that were not normally distributed (e.g., catecholamine data due to several missing observations) a Wilcoxon signed

rank test was performed comparing changes from baseline with each pacing mode. Simple linear regression analysis was used to test for correlations between each of the hemodynamic variables and forearm vascular resistance, observed before phentolamine and analyzed for each pacing mode. The measurements were first adjusted for baseline values. Differences between individual pacing modes were tested by means of repeated measures analysis of variance for each pacing mode, and for measurements before and after phentolamine.

Probability levels <0.05 were considered to be significant. Results are presented as mean ± standard error of the mean.

RESULTS

Patient population: We studied 16 men who ranged in age from 38 to 72 years with a mean age of 60 ± 3 years. The mean ejection fraction was 51 ± 2%. Six patients had no underlying organic heart disease, 3 patients had coronary artery disease without a history of myocardial infarction, 7 patients had coronary artery disease with a previous myocardial infarction and 8 patients had mild systolic hypertension. The reasons for electrophysiology study were syncope in 6 patients and ventricular arrhythmias in 10 patients. Two patients were receiving amiodarone at the time of study and 2 were receiving procainamide. The mean heart rate during sinus rhythm before the pacing protocol was 70 ± 3 beats/min. Only 3 patients had retrograde conduction with V-A intervals of 200, 250 and 260 ms.

Hemodynamics: At the beginning of the protocol the mean arterial pressure was 94 ± 2 mm Hg and after phentolamine infusion the mean arterial pressure was 96 ± 2 mm Hg (difference not significant). A significant increase in mean arterial pressure was observed with atrial pacing both before and after phentolamine but no significant change in mean arterial pressure with ventricular and V-A pacing occurred before phentolamine was given (Tables I and II, Figure 1). There was a significant decrease in mean arterial pressure with both ventricular and V-A pacing after phentolamine. One patient had a decrease in mean arterial pressure of >10 mm Hg during ventricular (V-A conduction intact) and V-A pacing. This patient had the smallest increase in forearm vascular resistance with both ventricular and V-A pacing.

There were no significant changes in mean arterial pressure among the baselines preceding each of the pacing protocols.

The changes in mean right atrial, mean pulmonary artery and mean pulmonary capillary wedge pressures and cardiac output with each pacing mode before and after phentolamine are listed in Tables I and II. Phentolamine infusion did not alter hemodynamics significantly for any pacing mode. The decrease in cardiac output seen with ventricular and V-A pacing was accompanied by a decreased pulse pressure, which was especially marked with V-A pacing.

Humoral responses: The baseline norepinephrine level was 183 ± 27 pg/ml (n = 14), epinephrine level was 85 ± 14 pg/ml (n = 12) and dopamine level was 78 ± 16 pg/ml (n = 12). During atrial and ventricular pacing, plasma catecholamine levels did not change significantly. The norepinephrine level increased to 232 ± 27 with V-A pacing ($p < 0.01$) whereas the epinephrine level and dopamine level tended to decrease (58 ± 8 and 49 ± 7 pg/ml, respectively, difference not significant).

Forearm vascular responses: Representative blood flow curves with numerical values of related hemodynamic data during each pacing mode are shown in Figure 2. Before phentolamine, forearm blood flow increased significantly with atrial pacing (0.4 ± 0.2 ml/min/100 ml forearm volume, $p < 0.05$ vs baseline). Changes in forearm blood flow during ventricular and

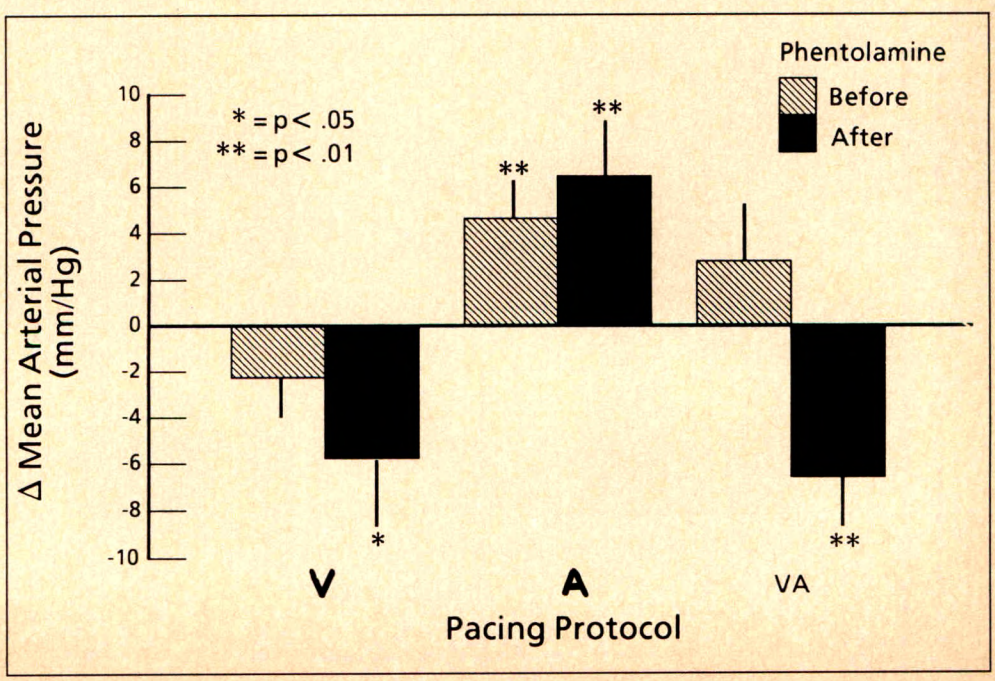


FIGURE 1. Group mean values (± standard error of the mean) for the change in mean arterial pressure (from baseline) during each pacing mode, before and after intraarterial phentolamine infusion.

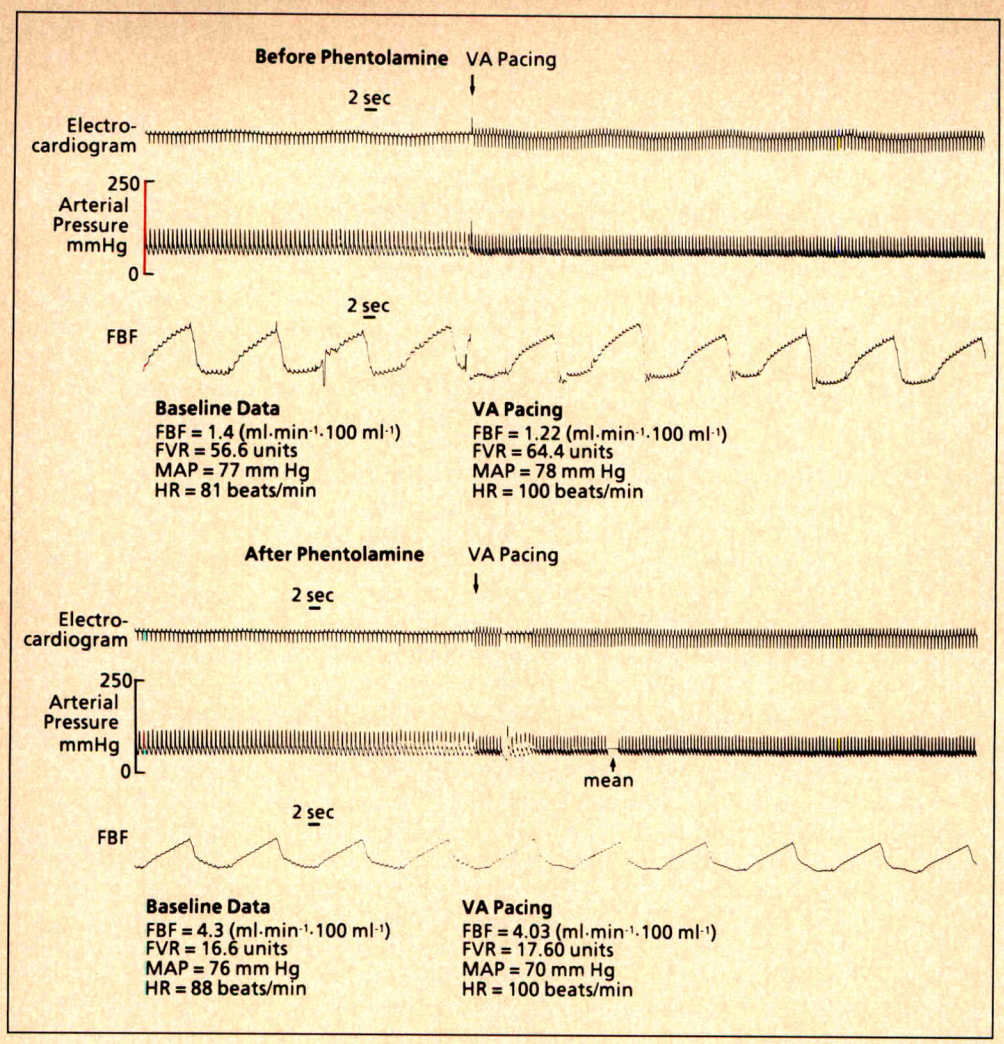


FIGURE 2. Analog data from patient showing recording of surface electrocardiogram, phasic arterial pressure (mm Hg) and foreman blood flow during ventriculo-atrial (V-A) pacing before (*top*) and after (*bottom*) phentolamine infusion.

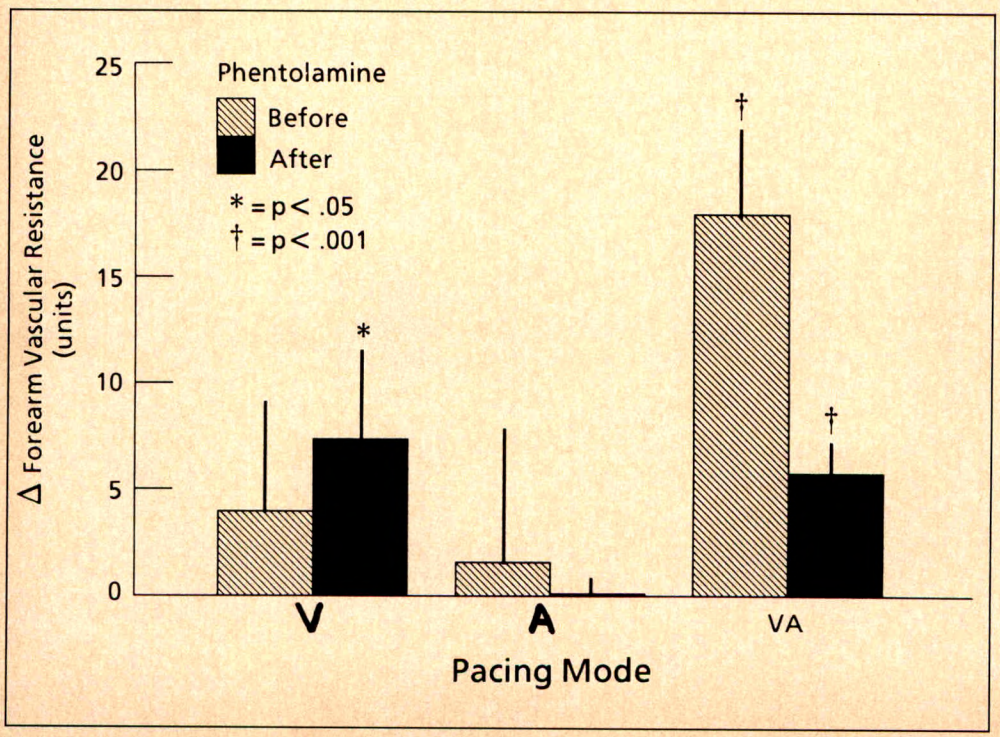


FIGURE 3. Group mean values (± standard error of the mean) for changes in forearm vascular resistance during each pacing mode before and after phentolamine infusion (p value = pacing mode change from baseline forearm vascular resistance).

V-A pacing were not significant (−0.4 ± 0.3 ml/min/100 ml and 0 ± 0.5 ml/min/100 ml, respectively). Forearm vascular resistance increased significantly with V-A pacing alone (18 ± 4.1 U, $p < 0.001$ vs baseline), whereas changes during ventricular (4.0 ± 3.3 U) and atrial pacing (1.6 ± 5.1 U) were not significant. During ventricular pacing, 3 patients had intact V-A conduction (V-A interval = 230 ± 30 ms) and had an increase in forearm vascular resistance of 14.4 ± 11 U. Two of these 3 patients had the largest increases in forearm vascular resistance of any patients in the ventricular pacing group.

After intraarterial phentolamine, there was a mean 3.5 ± 0.9-fold increase in forearm blood flow. The increase in forearm blood flow ranged from 1.5 to 5 times its basal value. After phentolamine infusion, forearm blood flow decreased significantly with ventricular (−1.6 ± 0.7 ml/min/100 ml forearm volume, $p < 0.05$) and V-A pacing (−2.3 ± 0.8 ml/min/100 ml forearm volume, $p < 0.01$). Forearm blood flow increased (0.5 ± 0.2 ml/min/100 ml, $p < 0.01$ vs baseline) significantly during atrial pacing. There was a significant increase in forearm vascular resistance with ventricular (7 ± 4.1 U) and V-A (5.8 ± 1.5 U) pacing ($p < 0.05$ and $p < 0.001$ vs baseline, respectively) (Figure 3).

Comparing changes in forearm vascular resistance with each pacing mode before and after phentolamine, only the changes that occurred with V-A pacing were significantly different. The responses of all patients studied before and after phentolamine are shown in Figure 4. The mean Δ forearm vascular resistance decreased from 18 ± 4.1 U with V-A pacing before phentolamine to 5.8 ± 1.5 U after phentolamine ($p < 0.001$, before vs after phentolamine), or a 67% decrease in forearm vascular resistance after phentolamine infusion. The changes in forearm vascular resistance were significantly different for ventricular versus atrial pacing modes ($p < 0.06$) and atrial versus V-A pacing modes ($p < 0.001$).

Time course: In 8 patients adequate curves of forearm blood flow during V-A pacing were available, which allowed calculation of forearm vascular resistance during the first and last 30 to 45 seconds. In all patients there was an immediate decrease in pulse pressure after the onset of V-A pacing. The forearm vascular resistance was 75% of its final value within the first 30 to 45 seconds (e.g., the first 3 to 5 curves measured).

Correlation of vascular responses to hemodynamic variables: The change in forearm vascular resistance during V-A pacing was poorly predicted by the changes in hemodynamic variables. The change in forearm vascular resistance did correlate well with the decrease in systolic arterial pressure ($r = 0.65$, $p < 0.01$) occurring with V-A pacing.

DISCUSSION

Our major finding is that forearm vascular responses to V-A conduction (pacing induced), but not ventricular pacing (with absent retrograde conduction), at 100 beats/min are mediated largely by activation of α-adrenergic receptors. The changes in vasomotor tone occurred within 30 seconds and may be assessed by forearm venous occlusion plethysmography in the electrophysiology laboratory. These changes in sympathetic tone to a regional vascular bed were correlated with systolic arterial pressure, but not with other hemodynamic changes, suggesting these vascular responses are largely mediated by arterial baroreceptors.

The presence of V-A conduction may play a role in causing pacemaker syndrome and may facilitate the induction of tachyarrhythmias.[10–12] Thus, it is important to define both hemodynamic alterations and regional changes in vasomotor tone that may not be evident when only systemic hemodynamics and total peripheral resistance are measured. There are no previous human studies that have systematically addressed this issue to define autonomic responses to V-A conduction that may importantly influence the occurrence of pacemaker syndrome as well as ventricular tachyarrhythmias.

Previous investigators have evaluated hemodynamic responses to V-A conduction in both humans and animals.[6,7,13,14] These studies have shown that atrial contraction plays an important role in maximizing cardiac output at rest, especially in patients with relatively normal ventricular function. The hemodynamic findings in our study confirm these observations.

Neurohumoral responses to ventriculo-atrial pacing: We sought to determine whether the autonomic responses to ventricular pacing at 100 beats/min, a pacing rate at which programmed electrical stimulation is often

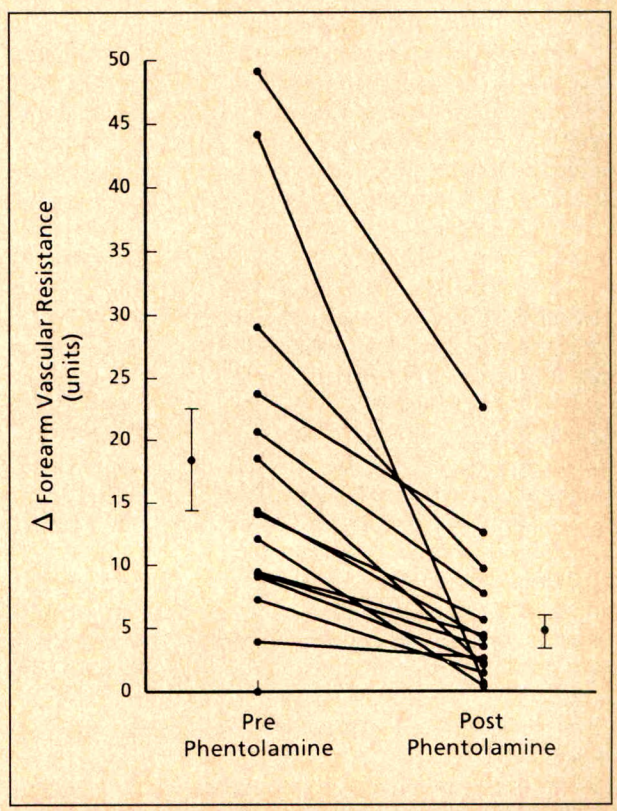


Figure 4. Individual values of forearm vascular resistance for each patient measured before and after phentolamine infusion.

performed, differed depending on the presence or absence of retrograde V-A conduction. First, elevated plasma norepinephrine levels were observed only during V-A pacing. This indicates an increase in sympathetic neural activity that was absent during ventricular or atrial pacing. Changes in plasma norepinephrine may not always reflect changes of efferent sympathetic nerve activity, as they are also influenced by rates of norepinephrine clearance in different vascular beds.[15–17] Steady-state changes in norepinephrine are linearly related to sympathetic nerve activity in humans although they may not correlate closely during nonsteady-state conditions.[15]

Gross hemodynamic changes and measurement of arterial pressure may not provide insight into the mechanisms for sympathetic nervous system activation during V-A pacing. Because autonomic responses can be highly differentiated, important regional changes in vasomotor tone are better detected by regional blood flow measurements. Thus, venous occlusion plethysmography provides accurate measurement of changes in regional blood flow, and thereby reflects changes in vasomotor tone in the arm or leg.[8] Infusion of intraarterial phentolamine was performed to achieve regional α blockade, demonstrating that α-adrenergic receptors are involved in mediating sympathetic vasoconstriction.[18] Our study highlights the importance of directly measuring reflex vascular responses to different pacing modes as a more direct estimate of autonomic responses. This approach is clearly superior to simply measuring systemic hemodynamics that may provide little direct insight into autonomic changes.

Limitations: To better assess the hemodynamic and vascular responses to each mode of pacing, we selected a homogenous patient population with minimal heart disease. Our results in this patient population may not apply to patients with more severe degrees of cardiac dysfunction.[19] It seems likely that such patients may be more susceptible to hypotension with V-A pacing, because of impaired sympathetically mediated vasoconstriction. Secondly, we chose a V-A interval of 125 to 150 ms during V-A pacing. The duration of V-A interval during pacing may influence neurohumoral activation. Moreover, different degrees of sympathetic activation may occur during V-A pacing at different V-A intervals. Finally, changes in sympathetic tone with V-A conduction may be more marked depending on the magnitude of volume depletion or patient position (supine vs upright) due to cardiopulmonary and arterial baroreflex activation or deactivation.

Clinical implications: During programmed electrical stimulation, retrograde V-A conduction may occur. Many factors may affect the presence or absence of retrograde V-A condution. In several studies, 40 to 70% of patients demonstrated V-A conduction with a V-A interval ranging from 100 to 300 ms (201 ± 53).[20] In patients with retrograde V-A conduction during ventricular pacing, subsequent sympathoexcitation may lead to a sufficiently altered autonomic milieu to contribute to the induction of ventricular tachycardia in patients with suitable substrates.[21–23] Many factors may contribute to arrhythmogenesis, and the presence or absence of V-A conduction is an additional one.

Pacemaker syndrome is a vaguely defined condition ranging from dizzy spells and syncope to postural hypotension.[24,25] These symptoms are felt to be secondary to atrial contraction occurring during ventricular systole with ventricular pacing. This syndrome is seen primarily in patients with V-A conduction.[20,26–28] During retrograde V-A conduction, there is a decrease in systolic pressure that is sensed by arterial baroreceptors, resulting in heightened sympathetic neural tone and increased norepinephrine. These changes result in increased α-mediated vasoconstriction.

These experiments provide clear evidence in patients without significant cardiac dysfunction that in the supine position, regional vasomotor tone is increased during V-A conduction. Our observations shed light on the mechanism of "pacemaker syndrome" that occurs, due to retrograde atrial activation. In the upright position, blood is pooled in the extremities and arterial baroreflexes are activated to maintain arterial pressure in the face of decreased venous return. Under these circumstances, patients with retrograde V-A conduction will have further activation of arterial baroreceptors. In some patients, pacemaker syndrome may be due to the inability to further augment sympathetic tone in the face of these 2 stimuli. Finally, these vascular responses may be further modified by drugs, underlying organic heart disease, volume status or autonomic defects.

Acknowledgment: We thank Debra Butler for assistance in preparation of the manuscript and Deborah Ravin for assistance with graphics.

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Assessment of Four Ambulatory Blood Pressure Monitors and Measurements by Clinicians Versus Intraarterial Blood Pressure at Rest and During Exercise

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The accuracy of 4 different ambulatory blood pressure (BP) monitors was assessed by comparing them to simultaneous intraarterial BP (contralateral brachial artery) during rest, isometric and dynamic (bicycle) exercise in 48 hypertensive patients undergoing invasive hemodynamic evaluation. The differences between the intraarterially determined BP and values obtained by the various monitors were then compared to differences between BP measured directly and by 2 clinicians using a standard mercury column in 10 additional hypertensive patients. The monitors studied were the Accutracker II (auscultatory with mandatory electrocardiographic gating), Colin ABPM 630 (auscultatory or oscillometric), Del Mar Pressurometer IV (auscultatory with optional electrocardiographic gating) and SpaceLabs 90202 (oscillometric). During rest, the differences between intraarterially and clinician-determined systolic and diastolic BP were 4 ± 8 and −4 ± 6 mm Hg, respectively. The Accutracker II and Colin ABPM 630 using the auscultatory method showed less disparity and closer limits of agreement (2 standard deviations of the mean difference) with intraarterial BP than the clinicians' measurements, whereas the other units showed similar or greater limits of agreement. During both isometric and dynamic exercise, mean BP differences between intraarterial and clinician determinations were similar to those at rest but the limits of agreement increased. The limits of agreement between intraarterial and monitor-derived BP also increased during exercise compared to differences observed at rest. The Accutracker II and Colin ABPM 630 using the auscultatory method had limits of agreement with intraarterial BP that were either similar to or less than the clinicians', whereas the Colin monitor using the oscillometric method and the Del Mar Pressurometer IV showed greater disparity. The SpaceLabs unit produced only error codes in 8 of 10 subjects during dynamic exercise. Thus, these data show that at rest, noninvasive ambulatory BP monitors are similar in accuracy to clinicians in BP determination but during exercise there are differences among the monitors that make some of them unsuitable for measurements while in motion.

(Am J Cardiol 1990;65:60–66)

In recent years there has been a proliferation of noninvasive ambulatory blood pressure (BP) monitors that have aided in diagnosis of mild and borderline hypertension[1] and the assessment of "office"—or "white-coat"—hypertension.[2–4] Most of the monitors determine BP by using standard auscultation of Korotkoff sounds via a microphone either taped over the brachial artery[5,6] or sewed into the BP cuff.[7,8] A minority of ambulatory monitors measure BP through perception of the oscillometric waves generated by the brachial artery during cuff deflation.[9] At present, ambulatory monitors may enter the market in the United States after review of a manufacturer's report that demonstrates that the recorder poses no safety hazard to a patient and is reliable. However, the definition of reliability and precision of a BP monitor is currently under considerable dispute, which has led to the formation of committees in both the United States and Europe to develop guidelines for clinically evaluating the recorders. In this report, we evaluated and compared the accuracy of 4 different types of ambulatory BP monitors in a hemodynamic laboratory where well-controlled intraarterial BP measurements were made at rest and during exercise. The differences observed between the intraarterial BP and a given monitor were then compared to differences between intraarterial BP and clinician-determined BP via a stethoscope and mercury column.

METHODS

Types of monitors: There were 4 types of monitors evaluated in the study (Table I). The Accutracker II, an auscultatory unit that uses electrocardiographic leads for R-wave gating with the Korotkoff sounds, was marketed in 1988 and then modified in 1989 to have a silent motorized pump. The Colin ABPM 630,[8] marketed in 1987, can measure BP by auscultation or oscillometry. The Colin unit has a carbon dioxide cartridge that releases gas for cuff inflation; thus, it is entirely silent during BP measurement. The Del Mar Pressurometer IV (Del Mar P-IV),[10] which became available in 1987, is an auscultatory recorder that does not require elec-

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trocardiographic leads for BP determination; however, they may be used optionally. The SpaceLabs 90202 monitor, available since 1987,[9] measures BP by oscillometry and has no microphone or electrocardiographic leads.

Subjects: Fifty-eight hypertensive patients participated in our study. All agreed to participate in the current study after formal explanation of the purpose of this validation project. Our study was approved as part of ongoing invasive hemodynamic studies at Haukeland Sykehus by the ethical committee of the University of Bergen. None of the patients was catheterized solely to provide data for this study. All patients were involved in several different long-term hemodynamic and pharmacologic studies such as those that have been conducted at this institution for >25 years.[11,12] Patients were excluded from the study if sequential opposite-arm BPs were not within ± 5 mm Hg for both the systolic and diastolic BP.

Blood pressure determinations with the ambulatory blood pressure monitors: The measurement of intraarterial BP was performed in the brachial artery as previously described.[11] A short, stiff polyethylene catheter with a diameter of 1 mm was introduced approximately 17 to 20 cm into the brachial artery. Minimal damping of fluid in the catheter occurs because the catheter is both short and stiff.[11] Intraarterial pressure was measured by an external transducer (Elema Schønander). Ten patients were studied with each of the monitors. One exception to this was with the Colin ABPM 630 using the oscillometric method because just 8 subjects were evaluated. The Del Mar P-IV was studied without electrocardiographic leads in 5 subjects and with the electrocardiogram in the other 5 subjects.

The BP monitors were placed on the opposite arm and great care was taken to make certain that both arms were at the level of the heart during the measurement. In each patient, there were 5 supine and 5 seated measurements at rest, 2 measurements during isometric exercise (1 minute of sustained handgrip), 5 recordings over 5 to 7 minutes of bicycle exercise (100 watts for five minutes) and 1 to 2 readings after exercise in the seated position. Both the monitor and the arm in which the monitor determinations were being made were placed on a separate table from the bicycle ergometer and buffered with a pillow to avoid most (but not all) of the mechanical vibrations associated with cycling.

While a research technician manually activated the monitors to measure BP (deflation rate varied from 3 to 5 mm/s depending on the unit), an investigator (WBW) hand scored the exact moments of cuff inflation, cuff deflation and cessation of the cuff deflation on the intraarterial pressure tracings. These were read later with the investigator blinded to the monitor readings. Because it is very unlikely that one will identify the exact beat on the tracing associated with the first and last Korotkoff sounds from the noninvasive measurement, the intraarterial BPs were determined by averaging the first 15 seconds after cuff deflation began for systolic BP and the last 15 seconds of cuff deflation for diastolic BP (the usual time for cuff deflation was 40 to 60 seconds). When there were large swings in intraarterial BP secondary to phenomena such as coughing or respiratory variation (seated position), the measurements were deleted from the analysis.

TABLE I Types of Ambulatory Blood Pressure Monitors Evaluated

Name of Monitor (Manufacturer)	Method of Blood Pressure Determination	Special Features
Accutracker II (Suntech Medical Instruments)	Auscultatory	ECG gating of R wave and K sounds
Colin ABPM 630 (Colin Medical Instruments)	Auscultatory/ Oscillometric	Carbon dioxide gas cartridges allowing for silent cuff inflation
Del Mar Pressurometer IV (Del Mar Avionics)	Auscultatory	Optional ECG gating
SpaceLabs 90202 (SpaceLabs)	Oscillometric	No microphone placement

ECG = electrocardiographic; K sounds = Korotkoff.

To determine the intraobserver error involved with the calculation of the intraarterial BP by the smoothing method noted before, 10 randomly selected beats within the 15-second period were evaluated against the hand-smoothed average (a hand-drawn line at the top of the arterial pressure waves as previously described[11]) for 20 randomly chosen systolic and diastolic pressures in different patients. The differences between hand-smoothed averages and individual beats were then assessed at the different levels of BP. This allowed for the determination of limits of agreement (and potential intraobserver variability) for the measurement of the intraarterial BP.

Blood pressure determinations with clinicians: In a fashion identical to that performed with the BP monitors, BP measurements at rest, handgrip and during bicycle exercise were made by 2 different skilled clinicians using a mercury column to compare with the intraarterial tracings. The clinicians (both with normal audiograms) alternated in the measurements, because simultaneous measurement with a teaching stethoscope proved to be too unwieldly for proper auscultation in the limited space available.

Statistical analyses: The group means for monitor versus intraarterial BP or clinicians vs intraarterial BP were examined using 2-tailed paired *t* tests. The data are reported as the mean ± standard deviation unless stated otherwise. The individual values of BP measured by the 2 different methods (e.g., clinician vs intraarterial BP) were assessed for mean differences at a given level of BP and the limits of agreement (2 standard deviations of the mean) were calculated as described by Bland and Altman.[13] This method of comparison has recently been considered statistically superior to simple visual plots of actual BP values and calculation of a regression line.[14]

The differences obtained between intraarterial BP and clinician-determined BP were compared with differences between intraarterial BP and the monitor-determined BP using an intergroup analysis of variance. For comparison between 2 groups, an unpaired 2-tailed *t* test was used.

TABLE II Blood Pressures Comparing the Measurements of the Clinicians and Various Monitors with Simultaneous Intraarterial Measurements

	Systolic BP	Diastolic BP
Measurements at rest		
Clinicians' BP	142 ± 12*	100 ± 10*
Intraarterial BP	146 ± 14	96 ± 9
Accutracker II BP	145 ± 21	88 ± 15*
Intraarterial BP	144 ± 21	91 ± 14
Colin ABPM 630 BP (oscillometric)	145 ± 16*	88 ± 9
Intraarterial BP	141 ± 15	88 ± 11
Colin ABPM 630 BP (Korotkoff)	139 ± 11	88 ± 10
Intraarterial BP	137 ± 9	88 ± 9
Del Mar P-IV BP	151 ± 23*	94 ± 16†
Intraarterial BP	145 ± 19	92 ± 13
SpaceLabs 90202 BP	142 ± 12*	93 ± 9*
Intraarterial BP	144 ± 12	90 ± 9
Measurements during isometric exercise		
Clinicians' BP	159 ± 20	100 ± 12*
Intraarterial BP	161 ± 24	95 ± 12
Accutracker II BP	159 ± 22	103 ± 16†
Intraarterial BP	163 ± 20	108 ± 16
Colin ABPM 630 BP (Korotkoff)	165 ± 22	101 ± 15†
Intraarterial BP	170 ± 20	97 ± 16
Del Mar P-IV BP	169 ± 21†	112 ± 17
Intraarterial BP	162 ± 19	111 ± 15
SpaceLabs 90202 BP	161 ± 8	107 ± 11
Intraarterial BP	159 ± 11	107 ± 10
Measurements during bicycle exercise		
Clinicians' BP	159 ± 20	100 ± 12*
Intraarterial BP	161 ± 24	95 ± 12
Accutracker II BP	186 ± 20	99 ± 12
Intraarterial BP	185 ± 29	98 ± 17
Colin ABPM 630 BP (oscillometric)	159 ± 19	97 ± 10*
Intraarterial BP	165 ± 14	93 ± 7
Colin ABPM 630 BP (Korotkoff)	167 ± 12	95 ± 12
Intraarterial BP	164 ± 13	92 ± 6
Del Mar P-IV BP	207 ± 26	92 ± 17*
Intraarterial BP	202 ± 29	108 ± 8

Handgrip BP measurements were not performed with the Colin oscillometric method.
Exercise BP measurements were attempted in all subjects with the SpaceLabs unit but were only successful in 2 of 10 individuals and were not included in the analysis.
* $p < 0.001$ vs intraarterial measurements; † $p < 0.01$ vs intraarterial measurements.
BP = blood pressure.

RESULTS

Precision of clinicians and intraarterial blood pressure: The differences for intraarterial and clinician BPs were not statistically different between the 2 clinicians at rest (4/−4 ± 8/6 for clinician A vs 4/−4 ± 9/5 mm Hg for clinician B, $p = 0.23$), during isometric exercise (3/−6 ± 8/5 for clinician A vs 5/−3 ± 7/6 mm Hg for clinician B, $p = 0.30$), or during bicycle exercise (3/−5 ± 11/8 for clinician A vs 2/−8 ± 12/8 mm Hg for clinician B, $p = 0.27$). The differences in the intraarterial BP and the 2 clinicians' BP data were therefore combined in the evaluation against the differences between intraarterial BP and monitor-derived values.

The limits of agreement were calculated for the method of hand-smoothed intraarterial BP over a wide range of BPs (118/75 to 220/120 mm Hg). The difference in the hand-smoothed intraarterial BP and individually calculated measurements over a 15-second period was −0.2 ± 3.1 for systolic BP and −0.6 ± 2.6 for diastolic BP. The limits of agreement (and extremes of error) between the 2 methods thus was ± 6 mm Hg for systolic BP and ± 5 mm Hg for diastolic BP. No statistical differences were found between systolic and diastolic BP and no systematic error at high or low BPs was found by regression analysis of the differences between hand-smoothed averages and individual beat-to-beat BPs. Thus, it is possible that the hand-smoothed method adds a modest amount of error into the calculation of intraarterial BP for individual measurements even though mean differences were quite small.

Agreement at rest and exercise: Table II lists the group mean BPs for the various monitors plus the clinicians' values versus the intraarterial BP. Group means between intraarterial and noninvasive measurements were relatively similar for the various monitors during rest and isometric exercise. During bicycle exercise, mean diastolic BP for the Del Mar P-IV was both statistically and clinically significantly different from intraarterial BP, whereas the other units were similar to each other.

Individual data showing the differences between intraarterial BP and noninvasively determined BP are shown in Figure 1. The limits of agreement between the intraarterial BP and clinicians (Figure 1) was −12 and 20 at rest and this increased during exercise. The average difference between intraarterial and clinician BP was approximately 4/−4.5 mm Hg for systolic and diastolic BP, respectively. Neither the clinicians nor the BP monitors displayed a systematic error at the lower or higher extremes of BP during rest; however, all monitors demonstrated greater limits of agreement during bicycle exercise than BP during rest (Figure 1).

In Figure 2, the mean difference and 1 standard deviation of the mean difference between intraarterial BP and the noninvasive BP measurements are shown for purposes of comparison. At rest, the Accutracker II and Colin ABPM 630 (using auscultatory method of BP measurement) had significantly less disparity with directly measured BP than the clinician determinations (−1 ± 5/3 ± 4 and −2 ± 7/0 ± 6 mm Hg for the Accutracker and Colin units, respectively, vs −4 ± 9/4 ± 6 mm Hg for the clinicians [$p < 0.001$ for all comparisons]). There were also significant differences between the Del Mar and SpaceLabs units with the clinicians but these were the result of having mean differences of opposite sign compared to the findings of the clinicians because the limits of agreement for these 2 monitors were greater rather than less than those for the clinicians (Figures 1 and 2).

In contrast, during isometric exercise, the Del Mar P-IV and SpaceLabs units had smaller mean differences (−1 ± 7 mm Hg and 0.5 ± 10 mm Hg, respectively, vs −5 ± 5 for clinicians, $p < 0.01$ for both comparisons) from intraarterial diastolic BP than the clinicians, but the limits of agreement were either similar or larger. The other monitors showed similar limits of agreement to the clinicians with intraarterial BP.

In the evaluations during bicycle exercise, the Accutracker II showed smaller differences with intraarterial diastolic BP than the clinicians' differences (−1 ± 2 vs −5 ± 7 mm Hg, $p < 0.001$). The Colin monitor showed

similar levels of difference during exercise to the clinicians, whereas the Del Mar P-IV showed significantly greater differences for both systolic and diastolic BP ($-5 \pm 25/14 \pm 15$ mm Hg vs $2 \pm 14/-5 \pm 7$, $p < 0.01$ for systolic and < 0.001 for diastolic BP).

Reliability during exercise: There were extremely few error codes (lack of the monitor to obtain a physiologically meaningful BP) for all of the monitors during rest. During isometric exercise, the incidence of error codes rose to $6 \pm 3\%$ and was similar among the monitors. During bicycle exercise, however, the incidence of error codes was 7% for the Accutracker II, 9% for the Colin ABPM 630 (oscillometric), 12% for the Colin ABPM 630 (auscultatory) and 7% for the Del Mar P-IV. None of these was significantly different from the others. In contrast, the SpaceLabs unit had an incidence of 82% error codes during bicycle exercise. Because there were only 18 readings obtained in 2 patients, the SpaceLabs monitor was not included in the analysis during bicycle exercise.

DISCUSSION

The intraarterial BP is generally accepted as the most accurate method of BP determination because fastidious calibration of the transducer (with a water column) is possible and every beat can be analyzed on a strip chart recording if necessary.[11,15] Conversely, indirect BP measurement by well-trained clinicians has

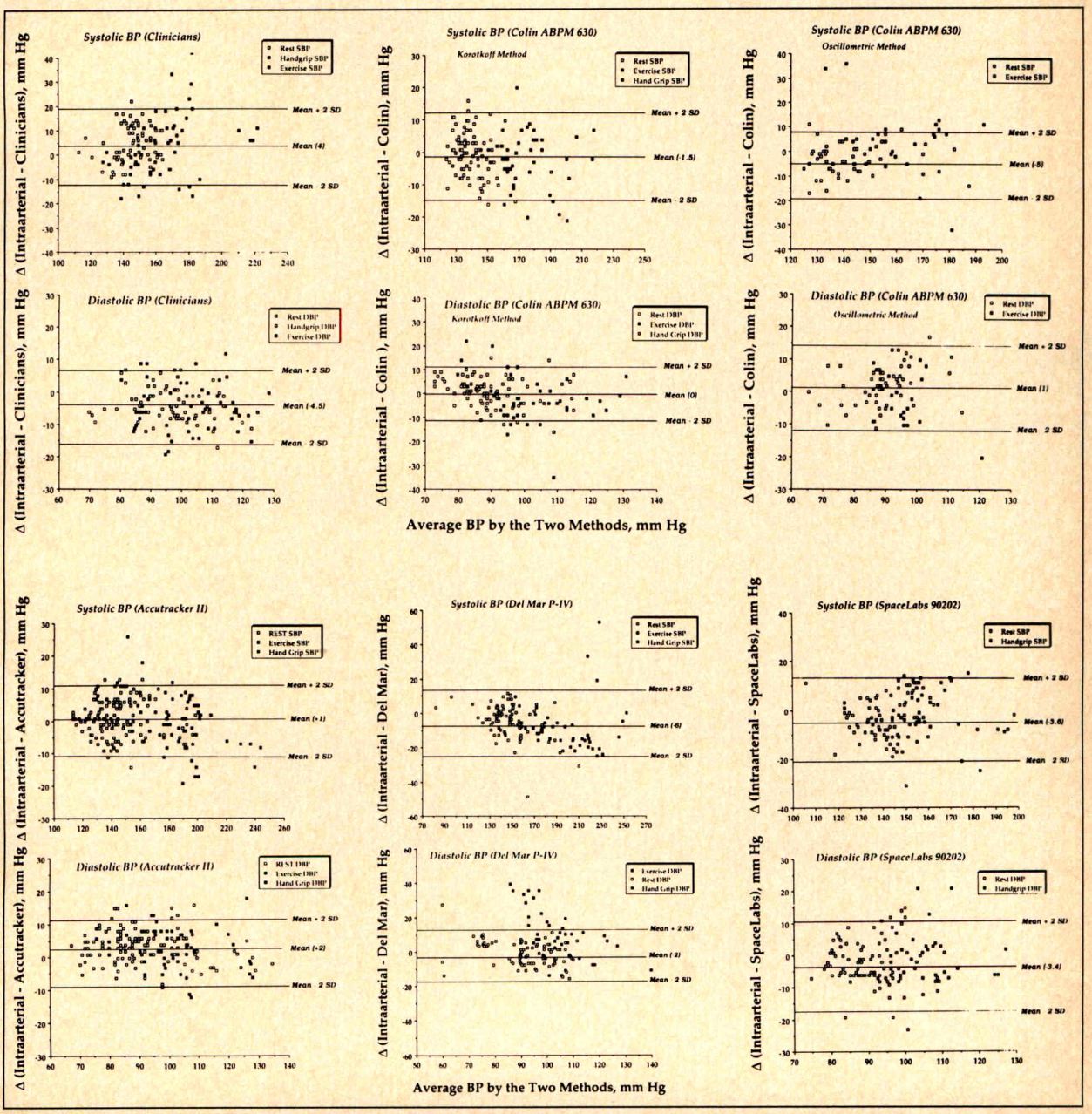


FIGURE 1. Scatter plots of the comparisons between individual differences in intraarterial BP and the clinicians and Colin ABPM 630 (*top*) and the Accutracker II, Del Mar Pressurometer IV and SpaceLabs 90202 (*bottom*). The *lines* show the limits of agreement for resting measurements.

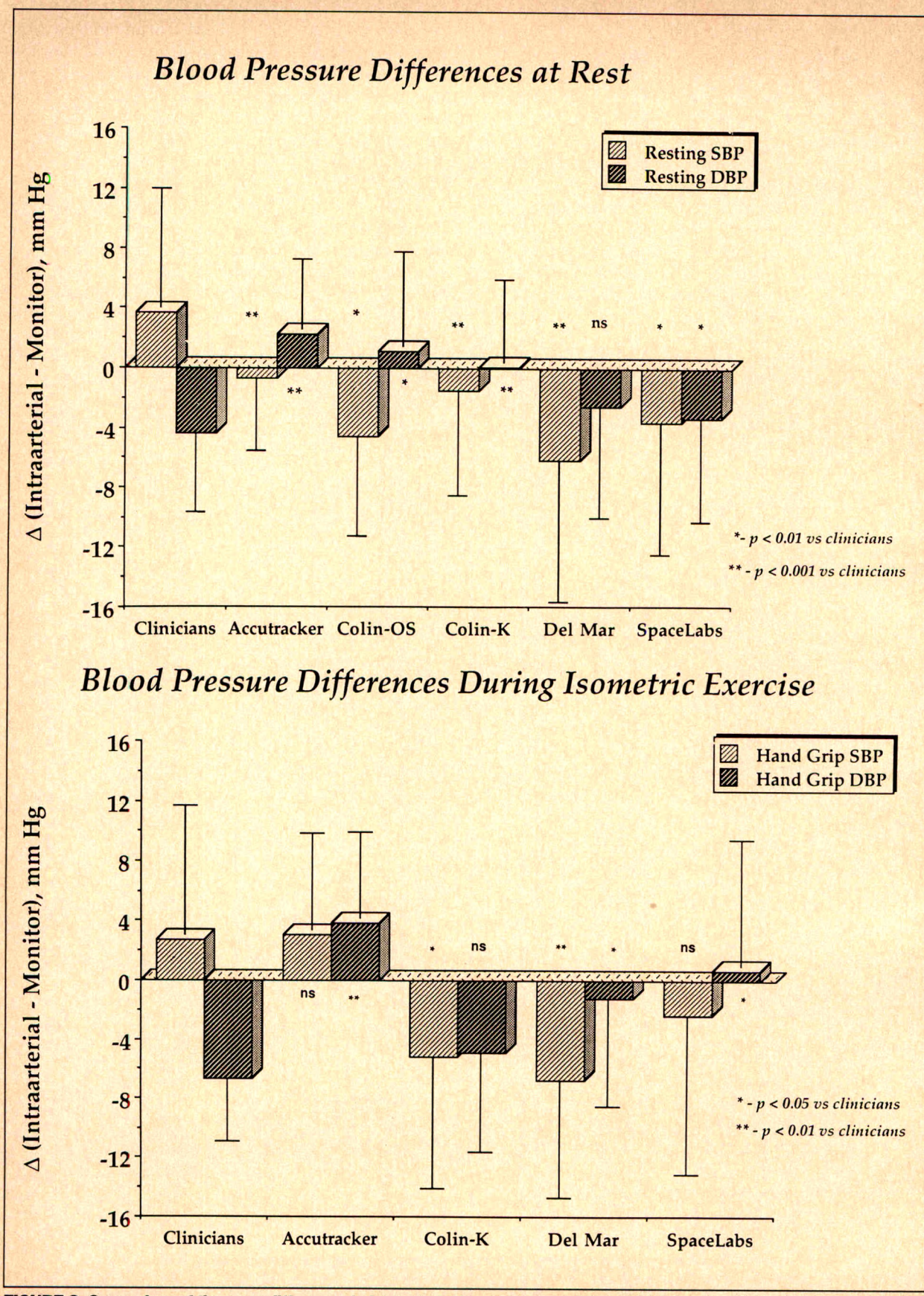


FIGURE 2. Comparison of the mean differences in intraarterial blood pressure (BP) and clinicians' and intraarterial BP and the various ambulatory BP monitors. D = diastolic; NS = difference not significant; S = systolic.

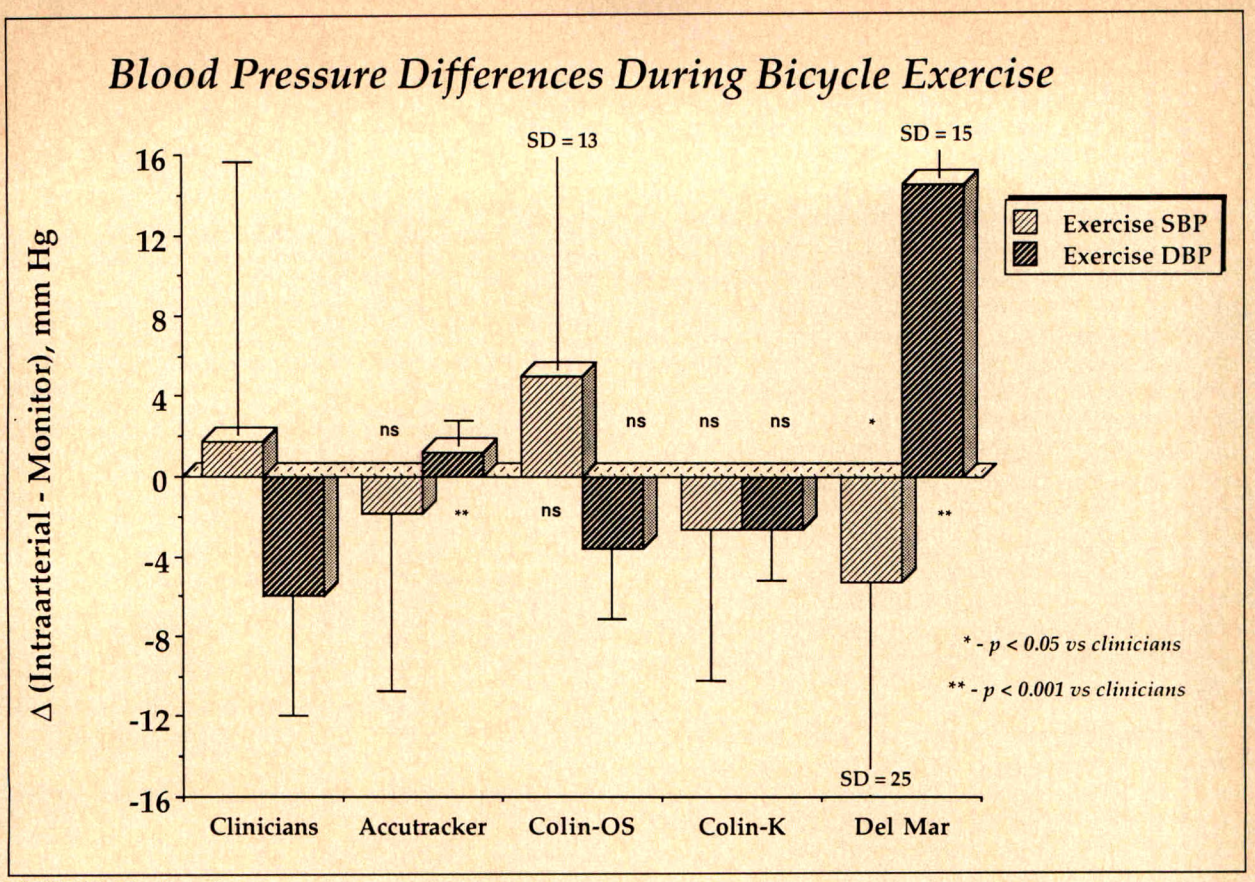


FIGURE 2. Continued.

been previously shown to be subject to large degrees of intraobserver variability that may be secondary to a number of causes, including observer bias.[16] Furthermore, the disparities between directly and clinician-determined BP are further exaggerated during exercise measurements, as motion artifact makes auscultation quite difficult in many individuals.[17,18] Thus, several investigators have recommended that all exercise BP measurements for research purposes be performed intraarterially. The data in our study suggest that this recommendation is probably correct, because individual scatter with clinicians (Figures 1 and 2) and even the best results with ambulatory BP monitors show unacceptable discrepancies with intraarterial BP.

In recent years, ambulatory BP monitoring has become important in both clinical research and practice. Unfortunately, widespread use of many of these monitors occurs before proper validation to assess precision and reliability for clinical use. The present study demonstrated that some of the newest and most widely used ambulatory BP monitors are similar to the clinician in accuracy at rest but may be quite misleading or even useless during ambulatory activities such as exercise. On the other hand, we found some reassurance that not all ambulatory BP monitors are alike, because some recorders were similar to or slightly more precise than the clinician BP readings.

Individual subjects can show large differences of variable sign among the BP values obtained by an ambulatory monitor or mercury column and intraarterial transducer (Figure 1), as has been reported previously.[7,8] There are several potential sources for the variability among the methods of BP determination that we have observed. First, there is an error in the perception of Korotkoff sounds by different clinicians, even if they are quite skilled, as has been demonstrated when 1 clinician's BP measurements are compared with another's using a teaching stethoscope.[8–10,15] Second, there is beat-to-beat variability in intraarterial pressure that occurs during the time it takes to obtain the indirect recording of BP so that the extreme limits of agreement with the hand-smoothing method are 5 to 6 mm Hg. Finally, there are errors from the recorders, especially notable during motion, in which ambient noise and the Korotkoff signal or oscillometric waves (depending on the type of monitor) cannot be distinguished from each other.

The precision of an ambulatory BP monitor during exercise or ambulation is difficult to assess. Most ambulatory BP monitors were not designed for use during vigorous exercise. However, bicycling causes far less mechanical artifact than an exercise treadmill and in the present study, the arm in which the noninvasive measurement was made was separated from the ergometry unit to avoid much of the motion artifact. The main outcome during isometric exercise was that the monitors were fairly good at following abrupt increases in BP (Figure 2), but that during dynamic exercise,

where there is always some arm movement, wide disparities with intraarterial BP occur (Figures 1 and 2). Thus, those monitors that show greater error during this form of cycling may be likely to demonstrate greater error during ambulation.

Our findings suggest that the best results with ambulatory BP monitors will be obtained by having the patients keep their arms entirely still during the actual measurement. There may be a clinically important issue at hand with this recommendation, although, as Brigden et al[19] pointed out, noninvasively measured BP during the daytime may be as much as 10/4 mm Hg lower than the average hourly intraarterial BP when activities are ceased to hold the arm still. Based on our data, with the Accutracker II and Colin ABPM 630 monitors (using auscultatory method of measurement), it should be possible to obtain readings during ambulation without the arm swinging, but it is unlikely that more vigorous exercise will allow for accurate readings. During use of the Del Mar P-IV and SpaceLabs 90202 monitors, total cessation of activity and arm movement is necessary for readings that would be similar in accuracy to that of a clinician.

Acknowledgment: Ambulatory BP monitors and computer software were supplied by CardioData Systems, Haddonfield, New Jersey (SpaceLabs 90202), Gallus-Plesner A/S, Oslo, Norway (Colin ABPM 630), VingMed A/S, Oslo, Norway (Del Mar P-IV), and Suntech Medical Instruments, Raleigh, North Carolina (Accutracker II).

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BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)

INDICATIONS AND USAGE
This drug product has been conditionally approved by the FDA for the prevention of angina pectoris due to coronary artery disease. Tolerance to the antianginal effects of nitrates (measured by exercise stress testing) has been shown to be a major factor limiting efficacy when transdermal nitrates are used continuously for longer than 12 hours each day. The development of tolerance can be altered (prevented or attenuated) by use of a noncontinuous (intermittent) dosing schedule with a nitrate-free interval of 10-12 hours.

Controlled clinical trial data suggest that the intermittent use of nitrates is associated with decreased exercise tolerance, in comparison to placebo, during the last part of the nitrate-free interval; the clinical relevance of this observation is unknown, but the possibility of increased frequency or severity of angina during the nitrate-free interval should be considered. Further investigations of the tolerance phenomenon and best regimen are ongoing. A final evaluation of the effectiveness of the product will be announced by the FDA.

CONTRAINDICATIONS
Allergic reactions to organic nitrates are extremely rare, but they do occur. Nitroglycerin is contraindicated in patients who are allergic to it. Allergy to the adhesives used in nitroglycerin patches has also been reported, and it similarly constitutes a contraindication to the use of this product.

WARNINGS
The benefits of transdermal nitroglycerin in patients with acute myocardial infarction or congestive heart failure have not been established. If one elects to use nitroglycerin in these conditions, careful clinical or hemodynamic monitoring must be used to avoid the hazards of hypotension and tachycardia.

A cardioverter/defibrillator should not be discharged through a paddle electrode that overlies a Transderm-Nitro patch. The arcing that may be seen in this situation is harmless in itself, but it may be associated with local current concentration that can cause damage to the paddles and burns to the patient.

PRECAUTIONS
General
Severe hypotension, particularly with upright posture, may occur with even small doses of nitroglycerin. This drug should therefore be used with caution in patients who may be volume depleted or who, for whatever reason, are already hypotensive. Hypotension induced by nitroglycerin may be accompanied by paradoxical bradycardia and increased angina pectoris.

Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

As tolerance to other forms of nitroglycerin develops, the effect of sublingual nitroglycerin on exercise tolerance, although still observable, is somewhat blunted.

In industrial workers who have had long-term exposure to unknown (presumably high) doses of organic nitrates, tolerance clearly occurs. Chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitrates from these workers, demonstrating the existence of true physical dependence.

Several clinical trials in patients with angina pectoris have evaluated nitroglycerin regimens which incorporated a 10-12 hour nitrate-free interval. In some of these trials, an increase in the frequency of anginal attacks during the nitrate-free interval was observed in a small number of patients. In one trial, patients demonstrated decreased exercise tolerance at the end of the nitrate-free interval. Hemodynamic rebound has been observed only rarely; on the other hand, few studies were so designed that rebound, if it had occurred, would have been detected. The importance of these observations to the routine, clinical use of transdermal nitroglycerin is unknown.

Information for Patients
Daily headaches sometimes accompany treatment with nitroglycerin. In patients who get these headaches, the headaches may be a marker of the activity of the drug. Patients should resist the temptation to avoid headaches by altering the schedule of their treatment with nitroglycerin, since loss of headache may be associated with simultaneous loss of antianginal efficacy.

Treatment with nitroglycerin may be associated with lightheadedness on standing, especially just after rising from a recumbent or seated position. This effect may be more frequent in patients who have also consumed alcohol.

After normal use, there is enough residual nitroglycerin in discarded patches that they are a potential hazard to children and pets.

A patient leaflet is supplied with the systems.

Drug Interactions
The vasodilating effects of nitroglycerin may be additive with those of other vasodilators. Alcohol, in particular, has been found to exhibit additive effects of this variety.

Marked symptomatic orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustments of either class of agents may be necessary.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No long-term animal studies have examined the carcinogenic or mutagenic potential of nitroglycerin. Nitroglycerin's effect upon reproductive capacity is similarly unknown.

Pregnancy Category C
Animal reproduction studies have not been conducted with nitroglycerin. It is also not known whether nitroglycerin can cause fetal harm when administered to a pregnant woman or whether it can affect reproductive capacity. Nitroglycerin should be given to a pregnant woman only if clearly needed.

Nursing Mothers
It is not known whether nitroglycerin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when nitroglycerin is administered to a nursing woman.

Pediatric Use
Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
Adverse reactions to nitroglycerin are generally dose-related, and almost all of these reactions are the result of nitroglycerin's activity as a vasodilator. Headache, which may be severe, is the most commonly reported side effect. Headache may be recurrent with each daily dose, especially at higher doses. Transient episodes of lightheadedness, occasionally related to blood pressure changes, may also occur. Hypotension occurs infrequently, but in some patients it may be severe enough to warrant discontinuation of therapy. Syncope, crescendo angina, and rebound hypertension have been reported but are uncommon.

Extremely rarely, ordinary doses of organic nitrates have caused methemoglobinemia in normal-seeming patients. Methemoglobinemia is so infrequent at these doses that further discussion of its diagnosis and treatment is deferred (see Overdosage).

Application-site irritation may occur but is rarely severe.

In two placebo-controlled trials of intermittent therapy with nitroglycerin patches at 0.2 to 0.8 mg/hr, the most frequent adverse reactions among 307 subjects were as follows:

	Placebo	Patch
Headache	18%	63%
Lightheadedness	4%	6%
Hypotension, and/or syncope	0%	4%
Increased angina	2%	2%

OVERDOSAGE
Hemodynamic Effects
The ill effects of nitroglycerin overdose are generally the result of nitroglycerin's capacity to induce vasodilatation, venous pooling, reduced cardiac output, and hypotension. These hemodynamic changes may have protean manifestations, including increased intracranial pressure, with any or all of persistent throbbing headache, confusion, and moderate fever; vertigo; palpitations; visual disturbances; nausea and vomiting (possibly with colic and even bloody diarrhea); syncope (especially in the upright posture); air hunger and dyspnea, later followed by reduced ventilatory effort; diaphoresis, with the skin either flushed or cold and clammy; heart block and bradycardia; paralysis; coma; seizures; and death.

Laboratory determinations of serum levels of nitroglycerin and its metabolites are not widely available, and such determinations have, in any event, no established role in the management of nitroglycerin overdose.

No data are available to suggest physiological maneuvers (e.g., maneuvers to change the pH of the urine) that might accelerate elimination of nitroglycerin and its active metabolites. Similarly, it is not known which, if any, of these substances can usefully be removed from the body by hemodialysis.

No specific antagonist to the vasodilator effects of nitroglycerin is known, and no intervention has been subject to controlled study as a therapy of nitroglycerin overdose. Because the hypotension associated with nitroglycerin overdose is the result of venodilatation and arterial hypovolemia, prudent therapy in this situation should be directed toward an increase in central fluid volume. Passive elevation of the patient's legs may be sufficient, but intravenous infusion of normal saline or similar fluid may also be necessary.

The use of epinephrine or other arterial vasoconstrictors in this setting is likely to do more harm than good.

In patients with renal disease or congestive heart failure, therapy resulting in central volume expansion is not without hazard. Treatment of nitroglycerin overdose in these patients may be subtle and difficult, and invasive monitoring may be required.

Methemoglobinemia
Nitrate ions liberated during metabolism of nitroglycerin can oxidize hemoglobin into methemoglobin. Even in patients totally without cytochrome b_5 reductase activity, however, and even assuming that the nitrate moieties of nitroglycerin are quantitatively applied to oxidation of hemoglobin, about 1 mg/kg of nitroglycerin should be required before any of these patients manifests clinically significant (≥ 10%) methemoglobinemia. In patients with normal reductase function, significant production of methemoglobin should require even larger doses of nitroglycerin. In one study in which 36 patients received 2-4 weeks of continuous nitroglycerin therapy at 3.1 to 4.4 mg/hr, the average methemoglobin level measured was 0.2%; this was comparable to that observed in parallel patients who received placebo.

Notwithstanding these observations, there are case reports of significant methemoglobinemia in association with moderate overdoses of organic nitrates. None of the affected patients had been thought to be unusually susceptible.

Methemoglobin levels are available from most clinical laboratories. The diagnosis should be suspected in patients who exhibit signs of impaired oxygen delivery despite adequate cardiac output and adequate arterial pO_2. Classically, methemoglobinemic blood is described as chocolate brown, without color change on exposure to air.

When methemoglobinemia is diagnosed, the treatment of choice is methylene blue, 1-2 mg/kg intravenously.

DOSAGE AND ADMINISTRATION
The suggested starting dose is between 0.2 mg/hr*, and 0.4 mg/hr*. Doses between 0.4 mg/hr* and 0.8 mg/hr* have shown continued effectiveness for 10-12 hours daily for at least one month (the longest period studied) of intermittent administration. Although the minimum nitrate-free interval has not been defined, data show that a nitrate-free interval of 10-12 hours is sufficient (see CLINICAL PHARMACOLOGY). Thus, an appropriate dosing schedule for nitroglycerin patches would include a daily patch-on period of 12-14 hours and a daily patch-off period of 10-12 hours.

Although some well-controlled clinical trials using exercise tolerance testing have shown maintenance of effectiveness when patches are worn continuously, the large majority of such controlled trials have shown the development of tolerance (i.e., complete loss of effect) within the first 24 hours after therapy was initiated. Dose adjustment, even to levels much higher than generally used, did not restore efficacy.

PATIENT INSTRUCTIONS FOR APPLICATION OF SYSTEM
A patient leaflet is supplied with each carton.

HOW SUPPLIED

Transderm-Nitro System*	Total Nitroglycerin in System	System Size	Carton Size
0.1 mg/hr	12.5 mg	5 cm²	30 Systems...NDC 57267-902-26
			**30 Systems...NDC 57267-902-42
			**100 Systems...NDC 57267-902-30
0.2 mg/hr	25 mg	10 cm²	30 Systems...NDC 57267-905-26
			**30 Systems...NDC 57267-905-42
			**100 Systems...NDC 57267-905-30
0.4 mg/hr	50 mg	20 cm²	30 Systems...NDC 57267-910-26
			**30 Systems...NDC 57267-910-42
			**100 Systems...NDC 57267-910-30
0.6 mg/hr	75 mg	30 cm²	30 Systems...NDC 57267-915-26
			**30 Systems...NDC 57267-915-42
			**100 Systems...NDC 57267-915-30

**Institutional Pack

*Rated release in vivo. Release rates were formerly described in terms of drug delivered per 24 hours. In these terms, the supplied Transderm-Nitro systems would be rated at 2.5 mg/24 hr (0.1 mg/hr), 5 mg/24 hr (0.2 mg/hr), 10 mg/24 hr (0.4 mg/hr), and 15 mg/24 hr (0.6 mg/hr).

Do not store above 86°F (30°C).

Summit Pharmaceuticals

Dist. by:
Summit Pharmaceuticals
Division of CIBA-GEIGY Corporation
Summit, New Jersey 07901

Printed in U.S.A.
C89-46 (Rev. 10/89)

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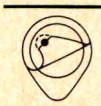
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• The only patch with an easy-open tab

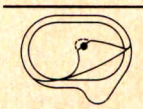
Easy to apply—
Easy to remove

Available in four convenient strengths
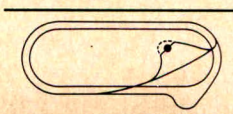
Patches shown are not actual size.
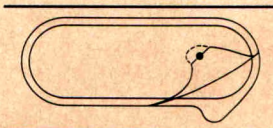


0.1 mg/hr...
Formerly designated as 2.5 mg/24 hr



0.2 mg/hr...
Formerly designated as 5 mg/24 hr



0.4 mg/hr...
Formerly designated as 10 mg/24 hr



0.6 mg/hr...
Formerly designated as 15 mg/24 hr

Concurrent Compliance Reduction and Increased Peripheral Resistance in the Manifestation of Isolated Systolic Hypertension

David S. Berger, MS, and John K.-J. Li, PhD

The hemodynamic mechanisms responsible for producing isolated systolic hypertension (ISH) in the elderly are generally attributed to a decrease in arterial compliance. However, no consistent theoretical or experimental model has been proposed for the production of ISH. This problem was investigated with the use of computer simulation of the modified Windkessel model, an often-used tool in the study of arterioventricular function. Aortic pressure ($P_a(t)$) and aortic flow ($Q_a(t)$) data were used to obtain the model parameters: peripheral resistance (Rs), arterial compliance (C) and characteristic impedance of the proximal aorta (Zo). Using $Q_a(t)$ as the input to the model, the effects of altered vascular properties on $P_a(t)$ were studied by changing these model parameters. Graded reductions of C (25, 50 and 75%) alone increased systolic pressure (P_s), but also decreased diastolic pressure (P_d) to values below those found in ISH. On the other hand, an increase in Rs of 25% along with a 50 to 75% increase in C resulted in percent changes in P_s and P_d that would result in ISH from a normal pressure level. These results were consistent for a wide range of pressures. Decreased arterial compliance alone is not always responsible for the production of ISH. Rather, isolated systolic hypertension is usually the result of greatly reduced arterial compliance along with a smaller but significant increase in peripheral resistance.

(Am J Cardiol 1990;65:67–71)

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Isolated systolic hypertension (ISH) is generally defined as a systolic pressure ≥160 mm Hg and a diastolic pressure <90 mm Hg[1] and has shown strong correlation with cardiovascular disease, especially coronary artery disease in Western subjects.[2–4] ISH can be found in both older and younger people.[5] ISH in the young is generally attributed to increased sympathetic tone, resulting in an abnormally short rapid ejection period, increased cardiac output and increased heart rate.[6] The mechanism causing ISH in the elderly has proven to be much more elusive.

Adamopoulos et al[5] showed that the total peripheral resistance was significantly greater in elderly patients with ISH compared to normotensive individuals in the same age group. Vardan et al[7] also demonstrated, through the use of thiazide therapy, the importance of elevated peripheral resistance in the genesis of ISH. Simon et al,[6] however, found only a significant decrease in compliance in elderly ISH patients compared to normal subjects, suggesting reduced arterial compliance as the main cause of ISH.[6,8] Smulyan et al,[9] however, demonstrated that decreased forearm compliance in ISH is the result of increased systolic pressure and not the cause. Results from intact dog experiments also suggested that decreased arterial compliance alone would not result in ISH.[10] Despite these hemodynamic findings and proposed mechanisms, no theoretical or animal model has been proposed that will consistently produce ISH.

We address the mechanism of ISH in the elderly only (vascular changes). We studied the problem by computer simulation of the arterial system with the modified Windkessel model,[11] using measured aortic flow as the input and aortic pressure as the output. With the model, we simulated alterations in vascular properties by changing the model parameters. This provided an excellent way to study the possible mechanisms for ISH in the elderly.

METHODS

Description of simulation: THE LUMPED ARTERIAL SYSTEM MODEL: The modified Windkessel model is shown in Figure 1. Zo, Rs and C represent the aortic characteristic impedance, total peripheral resistance and systemic arterial compliances, respectively. This model was chosen for its simplicity and accurate reproduction of arterial input impedance at low and high frequencies.[11–13] Moreover, its ability to accurately predict systolic and diastolic aortic pressures[14] makes it ideal for studying ISH.

State equations that describe the behavior of the model are:

$$\frac{dP_c(t)}{dt} = -\frac{1}{Rs \cdot C} P_c(t) + \frac{1}{C} Q_a(t) \quad (1)$$

and $$P_a(t) = P_c(t) + Zo \cdot Q_a(t), \quad (2)$$

where $Q_a(t)$ is the input aortic flow and aortic pressure $[P_a(t)]$ is the output. $P_c(t)$ is the compliance pressure. Equation (1) was solved numerically for $P_c(t)$ and $P_a(t)$ was then obtained.

Model parameters: CHARACTERISTIC IMPEDANCE: Zo was determined in the time domain by the instantaneous ratio of the change in aortic pressure (ΔP_a) to the change in aortic flow (ΔQ_a) in early ejection: ΔP_a is the difference between $P_a(t)$ at any time in early ejection and P_d, the diastolic pressure. ΔQ_a is simply $Q_a(t)$, because there is no flow at end-diastole. Therefore,

$$Zo = \left.\frac{P_a(t) - P_d}{Q_a(t)}\right|_{\text{early ejection.}} \quad (3)$$

Because wave reflection and other peripheral effects are small in early ejection, such as the first 60 ms, equation (3) provides a simple and reasonably accurate way to calculate Zo.[15–18] This method of determining Zo has been shown to compare favorably with high frequency average of the input impedance, which requires complex Fourier analysis.

PERIPHERAL RESISTANCE: Peripheral resistance (Rs) is defined as the ratio of mean arterial pressure ($\bar{P}_a$) to mean aortic flow ($\bar{Q}_a$), assuming left atrial pressure is small.

$$Rs = \bar{P}_a / \bar{Q}_a. \quad (4)$$

ARTERIAL COMPLIANCE: The diastolic aortic pressure decays exponentially with a time constant, τ, in accordance with the Windkessel model. Therefore, a simple expression relating pressure at end-diastole (P_d) and pressure at end-systole (P_{es}) can be written as

$$P_d = P_{es} \cdot e^{-t_d/\tau}, \quad (5)$$

where t_d is the diastolic time (Figure 2) and

$$\tau = Rs \cdot C \quad (6)$$

Solving equation (5) for C gives

$$C = \frac{-t_d}{Rs \cdot \ln(P_d/P_{es})}. \quad (7)$$

Data collection: Pressure and flow data from previously performed experiments on mongrel dogs of either sex with an average weight of 23 kg were used in the simulations. Experimental data were used in the simulations for a number of reasons; the first being that real flow waveforms would result in more realistic pressures, especially because ventricular ejection is very similar in patients with and without ISH.[6] A second reason is that using actual pressure and flow waveforms allowed us to derive actual Windkessel model parameters for use in the simulation. Most importantly, the numerical technique used to solve for the aortic pressure required digitized flow waveforms.

Briefly, each dog was anesthetized with intravenous sodium pentobarbital (25 mg/kg), trachea-intubated and artificially respired on an oxygen/room air mixture. A left thoracotomy was performed at the fifth intercostal space to expose the heart and great vessels. The ascending aorta was isolated for placement of a cuff-type electromagnetic flow probe for measurement of aortic flow. A catheter-tip blood pressure transducer was advanced from the femoral artery to the immediate vicinity of the flow probe for simultaneous measurement of aortic pressure. A standard lead electrocardiogram was also recorded. The frequency response of the pressure transducer was flat to well beyond 100 Hz. The flowmeter output low pass filter was 3 db down at 100 Hz. At this setting the amplitude response was flat within ± 5% to 30 Hz with a linear phase shift. The flow probes were statically calibrated against known volume flow rates in excised vessels.

Simultaneous recordings of $P_a(t)$, $Q_a(t)$ and the electrocardiogram were made on a 4-channel frequency modulated tape recorder (Vetter, C-4) and on a Gould electrostatic recorder at a paper speed of 100 mm/s with 10-ms time lines.

RESULTS

Figure 3 shows a typical pair of measured and the model-predicted aortic pressure waveforms. The Windkessel parameters for this example were: Rs = 3.39 mm Hg · s/ml, C = 0.40 ml/mm Hg and Zo = 0.17 mm Hg · s/ml; and for the remaining 2 dogs, respectively: Rs = 3.40, C = 0.35 and Zo = 0.23; and Rs = 3.68, C = 0.45 and Zo = 0.16. For this pressure waveform, the measured peak systolic pressure (P_s) to diastolic pressure (P_a) was 119/90 mm Hg. For the re-

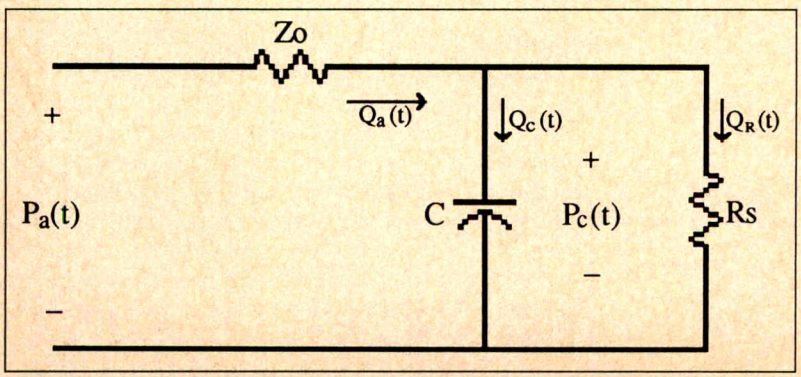


FIGURE 1. The modified Windkessel model of the arterial system. $Q_a(t)$ is the aortic flow and $Q_c(t)$ and $Q_R(t)$ are respective branch flows through C and Rs. $P_a(t)$ is the aortic pressure and $P_c(t)$ is the compliance pressure.

TABLE I Ps/Pd for Different Compliance and Rs Combinations*

	Compliance			
	−10%	−25%	−50%	−75%
Rs				
No change	120/86	122/84	128/77	149/59
15%	135/101	137/99	142/92	164/73
25%	145/111	146/108	152/102	173/82

* Actual values of C and Rs were 0.40 ml/mm Hg and 3.39 mm Hg · s/ml, respectively.
Rs = peripheral resistance.

maining 2, these were 103/69 and 131/105 mm Hg. The model-predicted values of P_s and P_d were 120/87 mm Hg for the first dog, 104/69 mm Hg for the second and 130/102 mm Hg for the third. Thus, the Windkessel model is reasonably accurate in predicting P_s and P_d.

Figure 4 shows the effects on the pressure waveform of a 50% decrease in C together with different increases in Rs (0, 15 and 25%). P_s and P_d values for a wide range of C and Rs for this same waveform are listed in Table I. The percent changes in P_s and P_d for this example were typical for all the data collected (Table II). Table II lists percent changes in P_s and P_d for 3 dogs with very different control values of P_s and P_d. (All percent changes are changes with respect to the predicted values of P_s and P_d using the control parameters.)

DISCUSSION

Blood pressure and the model parameters: The effects on blood pressure due to changes in arterial compliance and peripheral resistance are fairly well known.

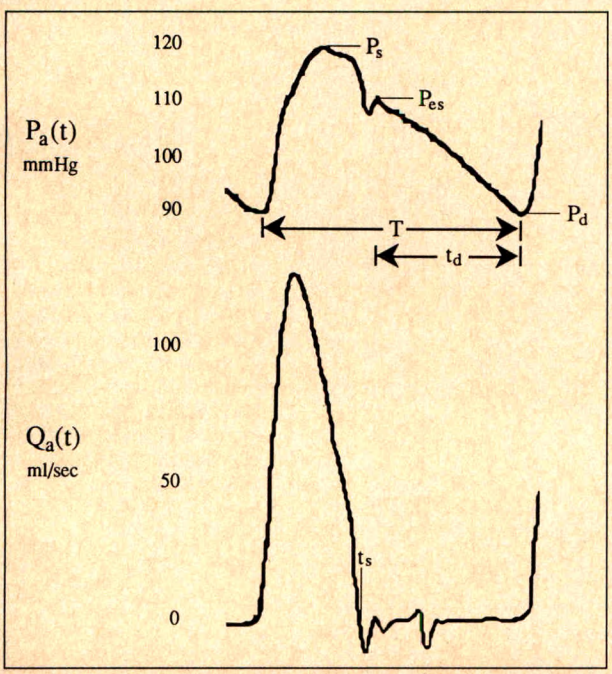


FIGURE 2. Aortic pressure ($P_a[t]$) and flow ($Q_a[t]$) waveform (dog 2). P_s, P_{es} and P_d are maximum systolic, end-systolic and end-diastolic pressures, respectively. T = period of the cardiac cycle; t_d = the diastolic time; t_s = the time at end-ejection.

TABLE II Percent Changes in Ps/Percent Changes in Pd*

	Compliance		
	−25%	−50%	−75%
Rs			
No change	1.4 ± 0.4 / −3.6 ± 0.8	5.6 ± 1.7 / −11 ± 2	21 ± 5 / −30 ± 6
15%	14 ± 1 / 13 ± 0.4	17 ± 1 / 6 ± 2	32 ± 6 / −13 ± 7
25%	22 ± 1 / 24 ± 0.2	25 ± 1 / 17 ± 2	40 ± 6 / −4 ± 4

* Values are mean percent differences ± standard deviation, from the predicted pressures using the actual values of compliance and Rs.
Abbreviation as in Table I.

An increase in Rs results in an increased mean pressure, and if C is unchanged, systolic and diastolic pressure would both increase. On the other hand, changing C should have no effect on $\bar{P}_a$, if the flow waveform remains unchanged. A decrease in C would therefore result in an increased systolic pressure and a decreased diastolic pressure. Specifically, the effect of decreasing C (higher P_s, lower P_d) and increasing Rs (higher P_s and P_d) would superimpose to result in a larger increase in P_s than P_d.[19,20] These effects on blood pressure, due to various combinations of altered C and Rs, have been shown to occur in isolated cat hearts beating into an artificial hydraulic load,[21] in isolated dog hearts beating into a computer-controlled arterial loading system[22] and in intact dog hearts.[10] What are unknown, however, are the quantitative changes in systolic and diastolic pressures due to changes in C and Rs. Can changes in arterial compliance and peripheral resistance affect blood pressure in such a way as to result in ISH, and if so, what are these changes?

Isolated systolic hypertension and the model parameters: Assuming that normal adult P_s is 120 mm Hg and P_d is 80 mm Hg, then ISH, according to our earlier definition, (160/95 mm Hg) requires at least a 33% increase in P_s and no more than an 18.75% increase in P_d. Therefore, according to the predicted pres-

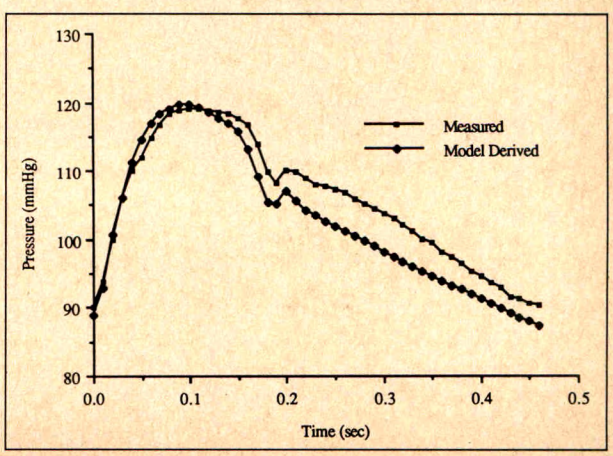


FIGURE 3. Measured (*square*) and model-derived (*diamond*) aortic pressure.

sures (Figure 4) and the percent changes (Table II), a decrease in C alone cannot cause ISH. A moderate decrease in C (25%) would not result in a high enough P_s, whereas an extreme reduction in C (75%) would not only cause P_s to increase to only 145 mm Hg but would also cause P_d to decrease far below normal (<80 mm Hg). On the other hand, a concurrent increase in Rs (of about 25%) along with a reduction in C (between 50 and 75%) could, at least in principle, cause ISH. Because the modified Windkessel model predicts P_s and P_d rather well, and keeping in mind that hypertension is, at best, ambiguous and that the levels of hypertension should not be considered clear cut,[23] we believe that similar changes of C and Rs in humans or laboratory animals will produce pressures falling into the range of ISH.

O'Rourke[20] has also pointed out that wave reflection could play a part in modifying the pressure contour. The Windkessel model lacks pulse transmission and did not allow us to examine this aspect. It is entirely possible that early wave reflections can augment systolic pressures in the aorta. The effect would be more pronounced in brachial arteries where conventional measurements are made. Thus, consideration of wave reflection may prove important if systolic pressure in ISH can be lowered by reduction in wave reflection, rather than by increasing arterial compliance through drug therapy.

The present study is model-based, using identical flows with different vascular parameters to predict changes in pressure. The decision to use control flows to model ISH was based on published patient data. In the studies of Simon et al,[6,8] patients with ISH had similar heart rates, left ventricular ejection times, cardiac indexes and ventricular ejections (slightly decreased in some) as patients without ISH. These data indicate that the flow is similar for ISH and normotensive patients and point to the vasculature for the mechanism of ISH. Whereas this statement may seem to disagree with experimental findings, in which altering Rs and C altered the flow waveform,[10,21,22] the situations are very different. The differences are mainly of time; changing Rs and C in the experimental studies was a relatively large and rapid perturbation, compared to changing vascular properties in humans, taking place over approximately 60 years. The cardiovascular system of an aging person could adapt to these relatively slow changes to maintain stroke volume. In the intact heart study[10] there simply was not sufficient time to allow for such adaptation. In the isolated heart studies,[21,22] all neural and humoral controls were (necessarily) cut off, further limiting the adaptive process. Despite these differences, the findings of Randall et al[10] seem to agree very well, at least qualitatively, with the model predictions.

Simon et al[6] showed that the only difference between older patients with and without ISH was that patients with ISH had a decreased compliance. However, Simon et al also showed a definite, although statistically insignificant, increase in Rs in patients with ISH over patients without ISH. In addition, Adamopoulos et al[5] reported a sizable increase in Rs in ISH patients, as did Vardan et al.[7] Normal aging has its effects on vascular properties as well, such that peripheral resistance increases and arterial stiffness increases, especially in the aorta, resulting in diminished compliance.[24–26] Therefore, we should expect that in normal, healthy people, P_s should gradually increase with age and P_d should re-

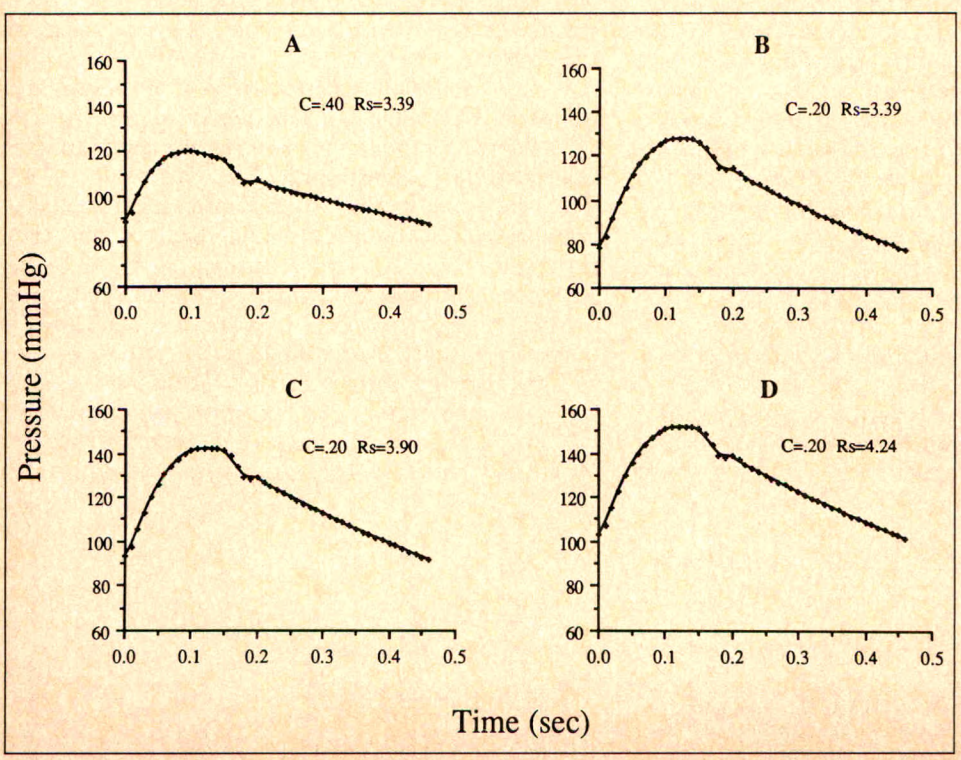


FIGURE 4. Predicted aortic pressures using different values of C (ml/mm Hg) and Rs (mm Hg · s/ml). *A*, measured values of C and Rs. *B*, 50% decrease in C, same Rs. *C*, 50% decrease in C, 15% increase in Rs. *D*, 50% decrease in C, 25% increase in Rs.

main rather constant, and this has been shown to be the case.[26] The data of Simon et al[6] indeed confirm that Rs in the older patients is much higher than Rs in younger patients. It is therefore possible that some of the Rs increase responsible for ISH (and decreased C) occurs naturally with age. Thus, ISH would likely be the result of an increase in peripheral resistance and a concurrent decrease in arterial compliance at levels greater than that normally seen in aging adults.

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Failure of Balloon Aortic Valvuloplasty to Result in Sustained Clinical Improvement in Patients with Depressed Left Ventricular Function

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Although balloon aortic valvuloplasty usually results in acute hemodynamic improvement, recurrent symptoms often occur within several months. The current study was designed to determine whether clinical characteristics, including invasive hemodynamic parameters of left ventricular (LV) performance, are predictive of short-term patient outcome. Eighty-one consecutive patients were prospectively enrolled in the study protocol. High-fidelity dual sensor micromanometer catheters, digital ventriculography and aortography and Fick cardiac output were measured before and immediately after balloon aortic valvuloplasty. Stroke work was defined from pressure-volume loops. The acute hemodynamic results obtained in patients with overall improved symptoms were compared to those with recurrent symptoms at 3 months. Fifty-three patients (65%) were improved at 3-month evaluation (group 1), whereas 28 patients (35%) had either returned to symptoms at baseline (17), had undergone aortic valve replacement (3) or had cardiac death (8). Compared to patients with improved symptoms, patients with recurrent symptoms demonstrated a lower cardiac output, higher LV end-systolic volume, decreased LV ejection fraction, diminished LV stroke work and decreased LV peak positive dP/dt. The final aortic valve area and change in aortic valve area did not predict which patients would develop recurrent symptoms. Stepwise logistic regression revealed that LV ejection fraction was the only independent predictor of overall status at 3 months ($p = 0.002$). Eighty-four percent of patients with an ejection fraction >45% were improved. In the group with an ejection fraction ≤45%, less than half of the patients demonstrated improved symptoms at short-term follow-up. Parameters of LV performance can accurately predict short-term patient outcome after balloon aortic valvuloplasty. Because patients with depressed baseline LV function are much less likely to have improved symptoms compared to patients with preserved LV performance, the clinical outcome of balloon aortic valvuloplasty appears primarily related to underlying LV function rather than any measurable change during the procedure.

(Am J Cardiol 1990;65:72–77)

Percutaneous balloon aortic valvuloplasty has been advocated for the treatment of severe aortic stenosis in a variety of patient groups.[1–3] Although the procedure is initially successful in reducing the transvalvular gradient, increasing the aortic valve area and improving symptoms, it is apparent that valvular restenosis is virtually inevitable within a variable period of time after balloon valvuloplasty.[4–6] However, persistent improvement in symptoms, in particular congestive heart failure and angina, may not be related to hemodynamic evidence of valvular restenosis.[4,7] The precise role and indications of balloon aortic valvuloplasty have yet to be defined in the treatment of calcific aortic stenosis. It is unknown which patients will receive long-term benefit from balloon dilatation and, conversely, which patients are least likely to derive even short-term improvement in symptomatology. Deterioration of symptoms may often occur within days to weeks after balloon aortic valvuloplasty despite initial hemodynamic evidence indicative of successful dilatation.[4,5] We determine whether either baseline demographic variables and invasive hemodynamic parameters of left ventricular (LV) performance or the resultant changes from the valvuloplasty procedure are predictive of overall symptomatic status as early as 3 months after balloon aortic valvuloplasty.

METHODS

Patient population: Eighty-one consecutive patients who underwent balloon aortic valvuloplasty at Duke University Medical Center were prospectively enrolled in the study protocol, which was previously approved by the institutional review board. Balloon aortic valvuloplasty was performed in patients who were at high risk for aortic valve replacement due to advanced age or the presence of other significant medical illnesses. Surgical consultation was obtained before the procedure in all patients. The mean age was 76 ± 8 years (range 53 to 89 years). Before the valvuloplasty, all patients had severe aortic stenosis and were symptomatic, with either New York Heart Association functional class III or IV congestive heart failure (74) or Canadian functional

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class III or IV angina (51), or a combination. Based on supravalvular aortography and echocardiography, the cause of aortic stenosis was presumed to be senile calcific aortic stenosis in 77 and bicuspid aortic stenosis in 4.

Valvuloplasty procedure: Balloon aortic valvuloplasty was performed by the retrograde technique in all patients. A single balloon (Mansfield, Inc.) of 20-mm and 23-mm maximal diameter was used in 62 and 6 patients, respectively. Thirteen patients had double balloon valvuloplasty performed with 20-mm and 10-mm balloons, respectively.

LV and aortic pressures were measured immediately before and after balloon valvuloplasty with dual sensor high-fidelity micromanometer pigtail catheters (Millar, Inc.). R-wave gated mask-mode digital subtraction left ventriculography and supravalvular aortography were obtained before and after balloon dilatation. Left ventriculography was performed in the 30° right anterior oblique projection using 45 cc of nonionic contrast media at 12 cc/s. Ventricular volumes were performed using area-length formulas and a regression equation derived from 10 previously calibrated human heart casts of known volume. Aortography was obtained in the left anterior oblique projection using 40 cc of contrast at 20 cc/s. Aortic regurgitation was graded 0 to 4+ by 2 independent observers using a standard angiographic grading scale.[8] LV and aortic images were recorded using an ADAC 4100-C Digital Radiography System interfaced to a GE-MPX L/U x-ray unit. Images were recorded using a 9-inch image intensifier mode into a 256 × 256 × 8 pixel matrix at 30 frames/s.

Before and immediately after balloon aortic valvuloplasty, oxygen consumption was measured with a metabolic cart (Sensormedics MMC Horizon System), pulmonary artery and systemic arterial oxygen content and saturation were determined and Fick cardiac outputs were generated. The effective aortic valve area was calculated by the Gorlin formula.[9]

Patient evaluation: Symptomatic status was evaluated by a physician interview and examination at baseline and at 3 months after the procedure unless a cardiac event occurred before that time. Endpoints were achieved when the patient died, underwent aortic valve replacement or was evaluated 3 months after the procedure.

Patients were divided into 2 groups based on overall status at the follow-up evaluation. Group 1 (53) consisted of patients whose overall status was improved and group 2 (28) included those patients with recurrent symptoms. Overall symptomatic status was considered improved if there was ≥1 grade improvement in either anginal or congestive heart failure functional class. Patients were classified as having recurrent symptoms if the anginal or congestive heart failure functional class either did not improve after the procedure, returned to baseline status or was worse than baseline, or if the patient incurred a cardiac event (e.g., sudden cardiac death or cardiac death).

Data analysis: Results are expressed as mean ± standard deviation. Statistical analysis between groups was performed using either a Wilcoxon rank-sum or signed rank test for continuous data or chi-square test for categorical data. A p value <0.05 was considered significant. Stepwise logistic regression analysis was used to test the independent value of baseline factors that were judged significant in the univariable analysis.

RESULTS

Patient outcome: Overall symptomatic status was evaluated in the 81 patients at follow-up and compared to baseline status (Figure 1). Fifty-three patients (65%) were improved at the 3-month evaluation (group 1). Recurrent symptoms (group 2) developed in 28 patients (35%). In the group of patients with recurrent symptoms, 17 returned to baseline symptoms, 3 underwent aortic valve replacement and 8 suffered a cardiac death. There were no significant differences between the 2 groups in age (group 1, 79 years [range, 53 to 89] vs group 2, 75 years [range, 61 to 85]), sex (group 1, 46% men vs group 2, 36% men) or presence of coronary artery disease (group 1, 49% vs group 2, 64%).

At 6 months, an additional 18 patients developed recurrent symptoms (12 returned to baseline, 1 underwent aortic valve replacement and 5 cardiac deaths occurred) (Figure 1). Thus, the probability of event-free survival was 65% at 3 months and 43% at 6 months. Due to the

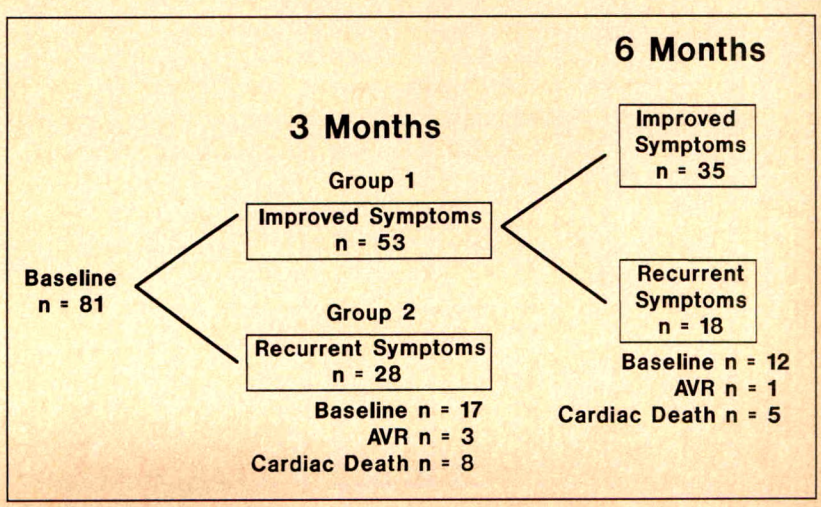


FIGURE 1. Patient outcome at 3- and 6-month evaluation. AVR = aortic valve replacement.

large number of events within the first 3 months, this endpoint was used to evaluate determinants of patient outcome.

Congestive heart failure was present at baseline in 74 patients and was improved by at least 1 functional class in 45 (61%) at the 3-month evaluation. Eighteen (24%) had recurrent symptoms to a similar degree as before balloon aortic valvuloplasty. Eight (11%) suffered a cardiac death and 3 patients (4%) required aortic valve replacement.

Fifty-one patients were in Canadian functional class III or IV angina before balloon aortic valvuloplasty. At 3 months follow-up, 32 (63%) were improved by at least 1 functional class. However, 12 (24%) had recurrent symptoms, 6 (12%) had a cardiac death and 1 (2%) required aortic valve replacement due to return of symptoms.

Hemodynamic results: In the total group of patients (81), balloon aortic valvuloplasty resulted in a significant decrease in left ventricular/aortic peak-to-peak and mean gradient from 70 ± 25 to 34 ± 18 mm Hg ($p < 0.0001$) and 57 ± 18 to 34 ± 13 mm Hg ($p < 0.0001$). Effective aortic valve orifice area increased from 0.57 ± 0.17 to 0.83 ± 0.21 cm^2 ($p < 0.0001$). Peak systolic aortic pressure was unchanged (138 ± 33 to 139 ± 30 mm Hg; $p = 0.29$). Left ventricular systolic pressure and end-diastolic pressure decreased from 207 ± 39 to 177 ± 32 mm Hg ($p < 0.001$) and 21 ± 9 to 17 ± 8 mm Hg ($p < 0.001$), respectively. Left ventricular ejection fraction increased from 46 ± 18 to 49 ± 18% ($p < 0.0001$). Aortic regurgitation increased by 1 grade in 4 patients and decreased by 1 grade in 5 patients. No patient had >1 grade change in the severity of aortic regurgitation.

The baseline hemodynamic results of the 2 groups were compared (Figure 2). Before balloon aortic valvuloplasty, LV/aortic peak-to-peak gradient was similar (group 1, 73 ± 23 mm Hg vs group 2, 64 ± 30 mm Hg) ($p = 0.10$), as was the aortic valve area (0.53 ± 0.16 vs 0.49 ± 0.18 cm^2) ($p = 0.11$). However, the mean aortic transvalvular gradient was 61 ± 17 in group 1, as opposed to 50 ± 19 in group 2 ($p = 0.02$). After the procedure, there continued to be no significant difference in peak-to-peak transvalvular gradient, nor was there a difference in the final aortic valve area between patients with recurrent symptoms and those with overall improved symptoms. Evaluation of patients with a final aortic valve area ≥1.0 cm^2 also did not allow distinction between the 2 groups. Seventeen (32%) patients with improved symptoms had a final aortic valve area ≥1.0 cm^2 as opposed to 4 (14%) with return of symptoms (chi-square = 3.0, $p = 0.08$).

The absolute change in transvalvular gradient and change in aortic valve area achieved with the procedure were evaluated for the 2 groups. The absolute decrease in aortic transvalvular gradient and increase in aortic valve area were similar for patients with improved

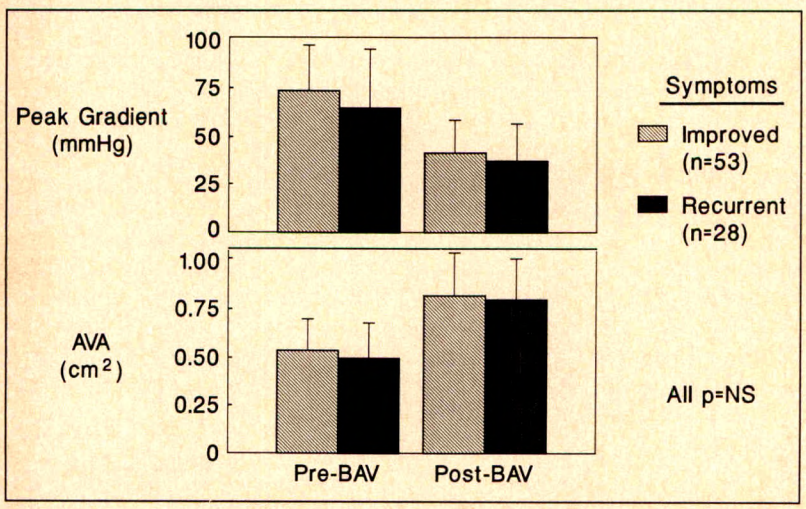


FIGURE 2. Aortic transvalvular gradient and aortic valve area (AVA) before and after valvuloplasty. No differences were observed between patients who improved at 3 months and those with recurrent symptoms. BAV = balloon aortic valvuloplasty.

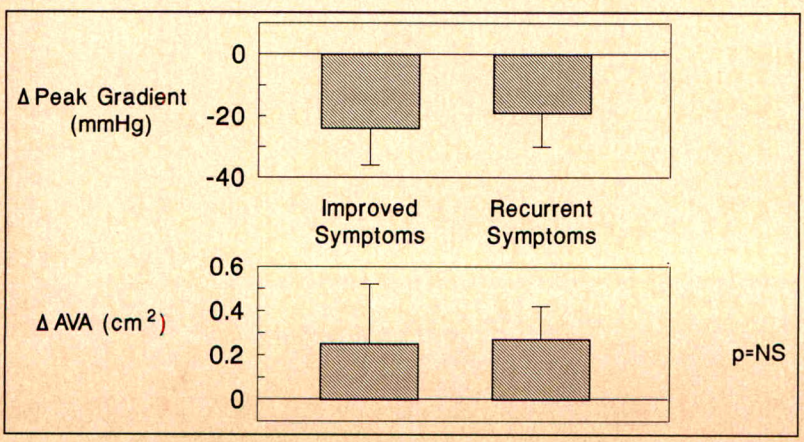


FIGURE 3. Change in aortic valve area (AVA) and transvalvular gradient. At 3 months, no differences were observed in the group with improved symptoms versus those with recurrent symptoms. NS = not significant.

symptoms versus those with recurrent symptoms (Figure 3).

Hemodynamic measures of LV systolic performance differed significantly in the 2 groups before balloon aortic valvuloplasty (Figure 4). Baseline Fick cardiac output was decreased in patients with early return of symptoms (3.8 ± 1.2 vs 4.5 ± 1.3 liters/min, p = 0.007). Additionally, patients with recurrent symptoms had a higher LV end-systolic volume both at baseline (98 ± 55 vs 68 ± 51 ml, p = 0.004) and after valvuloplasty (93 ± 49 vs 63 ± 47 ml, p = 0.001).

Patients with early return of symptoms demonstrated evidence of impaired systolic performance before the procedure as evidenced by decreased LV ejection fraction (35 ± 17 vs 52 ± 17%, p = 0.0002), low LV stroke work (11 ± 8 vs 14 ± 6 erg × 10^6, p = 0.007) and depression of LV peak positive dP/dt (1,397 ± 481 vs 1,765 ± 499 mm Hg/s, p = 0.003) (Figure 5).

Immediately after the procedure, there continued to be a significant difference between the 2 groups. Systolic function, as measured by LV ejection fraction, stroke work and peak positive dP/dt, was lower in patients with early recurrent symptoms (Figure 5).

Stepwise logistic regression analysis of baseline variables, including demographic and invasive hemodynamic parameters of LV function, revealed that only LV ejection fraction was an independent predictor of overall status at 3 months (p = 0.002).

Table I shows the close relation between baseline ejection fraction and symptomatic status at 3-month follow-up. The 2 groups were compared to determine the relative risk in patients with a depressed baseline

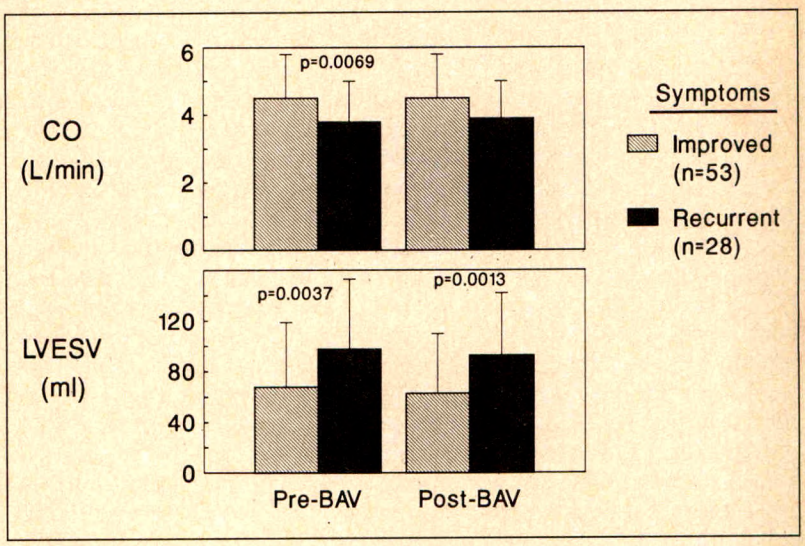


FIGURE 4. Hemodynamic parameters of left ventricular function at baseline and immediately after balloon aortic valvuloplasty (BAV). CO = cardiac output; LVESV = left ventricular end-systolic volume.

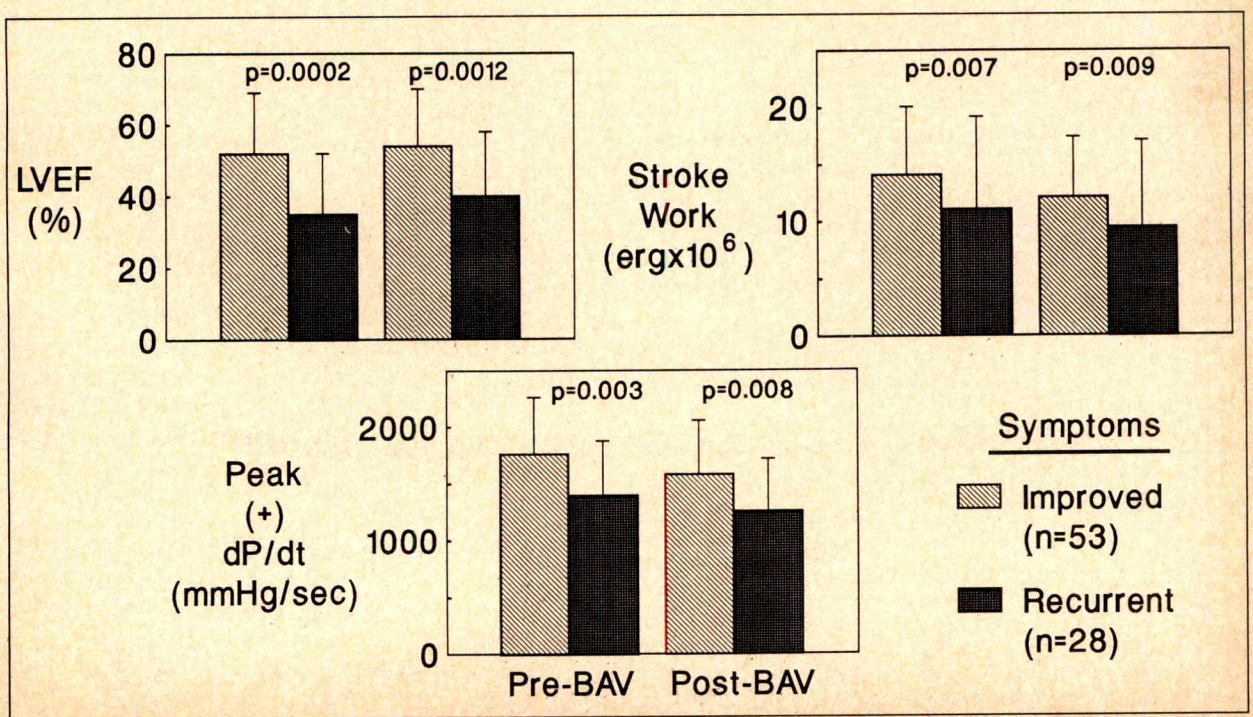


FIGURE 5. Hemodynamic parameters of left ventricular (LV) performance at baseline and immediately after balloon aortic valvuloplasty (BAV). EF = ejection fraction.

TABLE I Baseline Left Ventricular Ejection Fraction in Patients with Improved Versus Recurrent Symptoms

Baseline LVEF (%)	Improved Symptoms		Recurrent Symptoms	
	No.	%	No.	%
>45	37	84	7	16
≤45	16	43	21	57

Chi-square = 14.8; p <0.01; odds ratio = 6.9.

LV ejection fraction. Eighty-four percent of patients with an ejection fraction >45% were improved, and only 16% had early return of symptoms. With an ejection fraction ≤45%, less than half of the patients demonstrated improved symptoms at short-term follow-up. Five deaths occurred in patients with an ejection fraction <45%.

The probability of recurrent symptoms based on LV ejection fraction before the procedure is shown in Figure 6. A baseline ejection fraction ≥45% would predict that there is a 16% probability of recurrent symptoms at 3 months, as opposed to a 57% probability when ejection fraction is <45%, 63% risk at an ejection fraction ≤35% and 59% with an ejection fraction ≤25%.

In the 2 groups, there was no significant difference noted in the absolute change in LV ejection fraction (group 1, 2 ± 4% vs group 2, 4 ± 8%, p = 0.37), stroke work (group 1, 2.0 ± 2.7 vs group 2, 1.2 ± 2.2 erg × 10^6, p = 0.2), cardiac output (group 1, 0.0 ± 0.6 vs group 2, 0.1 ± 0.7 liters/min, p = 0.46) or LV peak positive dP/dt (group 1, 187 ± 250 vs group 2, 143 ± 158 mm Hg/s, p = 0.46). An acute increase in LV ejection fraction >5 units was noted in 6 of 53 (12%) patients with improved symptoms as opposed to 7 of 28 (25%) with early return of symptoms. Thus, the acute change in ejection fraction was not useful in predicting patient outcome.

DISCUSSION

We demonstrate that baseline parameters of LV performance can be used to accurately predict patient outcome after balloon aortic valvuloplasty. Patients with overall depression in LV systolic function are less likely to have improved overall status as early as 3 months after the procedure, whereas patients with preservation of baseline LV function are more likely to have a favorable short-term outcome.

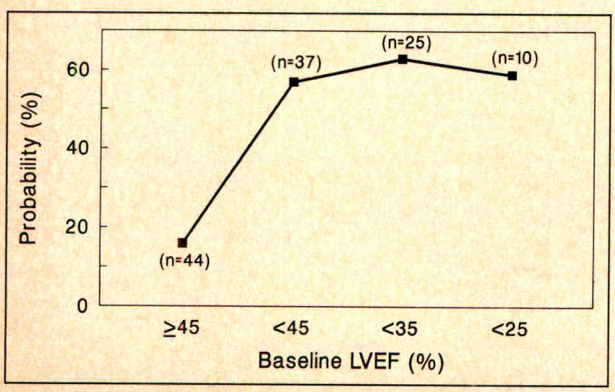


FIGURE 6. Probability of recurrent symptoms based on baseline left ventricular ejection fraction (LVEF).

Various measures of LV performance were used to assess systolic performance in this study. Despite the known effect of afterload on ejection phase indexes, the LV ejection fraction was the best independent predictor of patient outcome. Whereas more sophisticated measures of LV function, including stroke work and peak positive dP/dt, were univariably associated with short-term follow-up status, no other baseline parameter added to the predictive value of ejection fraction.

The absolute changes in transvalvular gradient and aortic valve area, along with the final aortic valve area, did not distinguish between the patients with recurrent symptoms and those with improved symptoms. Further, the acute improvement in LV ejection fraction did not identify a subgroup of patients who demonstrated improved symptomatic status. Although other preliminary studies have suggested that a final aortic valve area >1.0 cm^2 portends a good outcome from balloon aortic valvuloplasty,[10] this could not be consistently demonstrated in the current study. We used the most accurate methods to measure LV performance and aortic valve area, including dual sensor high-fidelity micromanometer catheters, Fick cardiac output and digital subtraction angiography. These differences in technique may account for the dissimilar results.

Carabello et al[11] demonstrated that mean aortic transvalvular gradient was an important predictor of outcome after aortic valve replacement. Although mean gradient in this study was univariably associated with short-term outcome after balloon aortic valvuloplasty, stepwise logistic regression did not confirm an independent predictive value of mean gradient. Furthermore, the peak LV to aortic gradient was similar in the 2 groups at baseline and immediately after the procedure.

In patients with depression of LV function or functional class IV congestive heart failure, aortic valve replacement has been associated with an increased perioperative mortality.[12–15] However, long-term survival, improvement in functional class and reversal of advanced LV dysfunction are often observed after aortic valve replacement. In general, LV performance appears to be linked to perioperative mortality rather than long-term survival after aortic valve replacement.

Balloon aortic valvuloplasty, although providing an acute increase in aortic valve area and an improvement in LV function, may not provide an adequate final effective orifice area to sustain symptomatic improvement even to 3 months in patients with associated LV pump dysfunction. Waller et al[16] have demonstrated that balloon valvuloplasty of nonrheumatic aortic stenosis results in aortic wall stretching with minimal cuspal injury. Thus, the overstretched aortic walls may recoil and may contribute to early clinical restenosis. The relief of valvular obstruction achievable when calcific aortic stenosis is dilated by balloon valvuloplasty is likely not sufficient in a dysfunctional left ventricle to result in ade-

quate reversal of intrinsic myocardial contractile depression.

Although LV ejection fraction has been shown to increase in 13 of 28 patients as reported by Safian et al,[17] this does not allow prediction of which subgroup of patients might respond to balloon aortic valvuloplasty. Further, we demonstrate that approximately 60% of patients with depressed LV function will experience early return of symptoms. Thus, whereas a small subset of patients with poor LV performance may be improved at 3 months, it appears that, overall, the procedure is generally ineffective in this group.

Our data agree with those of Sherman et al,[18] who also found a correlation between baseline ejection fraction and short-term clinical outcome. Our data extend these findings in a larger patient population with more extensive measures of LV performance, including stroke work and peak positive dP/dt.

Based on the lack of even short-term improvement in patients with intrinsic depression of LV function, it would appear that balloon aortic valvuloplasty should not be considered definitive therapy in this subset. Indications for balloon aortic valvuloplasty should continue to be limited to elderly patients at high risk for cardiac surgery due to comorbid disease.[19,20] In patients with New York Heart Association functional class IV congestive heart failure, balloon valvuloplasty clearly provides a short-term improvement in patient hemodynamics over several weeks, potentially lowering operative risk for aortic valve replacement. Balloon aortic valvuloplasty may be effectively used as a "diagnostic intervention" to identify those patients most likely to demonstrate improvement in LV function and contractility after aortic valve replacement.

As opposed to aortic valve replacement,[13–15] balloon aortic valvuloplasty does not appear to achieve an adequate reduction in transvalvular gradient and increase in aortic valve area to permit recovery of depressed LV function. Therefore, sustained symptomatic improvement in patients with severe depression of LV performance should not be expected. The degree of baseline LV dysfunction may be the primary determinant of clinical improvement after this procedure. Procedural events or the acute changes that occur after the procedure appear to have a minor influence on long-term clinical results.

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Effect of Isometric Exercise on Mitral and Aortic Regurgitation as Assessed by Color Doppler Flow Imaging

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Isometric exercise produces well-defined hemodynamic changes in normal and diseased states. However, the effect of isometrics on the degree of valvular regurgitation recorded by color Doppler flow imaging (CDFI) has not been reported. CDFI was therefore used to evaluate changes in valvular regurgitation in 34 patients, mean age 53 ± 16 years. Data were collected for 43 regurgitant lesions including 20 cases of aortic regurgitation and 23 cases of mitral regurgitation. Isometrics produced a significant increase in heart rate (71 to 83 beats/min) and blood pressure (132/64 to 153/70 mm Hg) in all patients ($p < 0.0001$). Regurgitant jet area by CDFI increased significantly in both aortic regurgitation (4.5 to 6.2 cm^2, $p < 0.0001$) and mitral regurgitation (6.2 to 8.2 cm^2, $p < 0.001$). Patients taking concurrent vasodilator or angiotensin-converting enzyme inhibitor therapy had similar responses to those not receiving long-term therapy. Thus, CDFI detects an increase in aortic and mitral regurgitant jet area induced by isometric exertion. The change in CDFI jet area with handgrip demonstrates the influence of loading conditions on the size of a regurgitant jet area, and suggests that isometric exertion may increase the magnitude of mitral and aortic regurgitation.

(Am J Cardiol 1990;65:78–83)

Isometric exertion is a common activity with well-recognized hemodynamic effects.[1–9] The response to handgrip exercise has been used to evaluate left ventricular function both in normal subjects and patients with various forms of heart disease, including valvular regurgitation.[10–17] Nevertheless, the effect of isometrics on the magnitude of valvular regurgitation remains uncertain.

Color Doppler flow imaging (CDFI) is a recently developed imaging modality that enables visualization of the flow disturbance in patients with valvular regurgitation.[18,19] Initial data have indicated that CDFI enables the semiquantitation of valvular regurgitation noninvasively.[20–23] Specifically, available studies have revealed a general correlation between regurgitant jet area by CDFI and the degree of regurgitation as assessed by angiography.[24] We designed this study to examine the effects of isometric exercise on the size of the regurgitant jet due to valvular heart disease using CDFI.

METHODS

Study population: CDFI was performed in a prospective fashion in a group of patients in whom the presence of valvular regurgitation was documented by physical examination, conventional Doppler studies or cardiac catheterization. Patients were selected for inclusion based, in part, on the attainment of a high quality CDFI examination. Acceptable data were obtained for 43 regurgitant lesions in 34 patients, which included 20 cases of aortic regurgitation and 23 cases of mitral regurgitation. The study group was composed of 16 women and 18 men with a mean age of 53 ± 16 years. The regurgitant lesions were due to multiple etiologies including: dilated cardiomyopathy (12), rheumatic heart disease (9), ischemic heart disease (8), congenital malformations (4) and treated endocarditis (1). All patients were in sinus rhythm and clinically compensated. Sixteen patients were known to be receiving concomitant vasodilator therapy or angiotensin-converting enzyme inhibitors.

Instrumentation: All CDFI studies were performed by a single operator with the patient in the left lateral decubitus position using commercially available or prototype instruments operating with either 2.5- or 3.5-MHz transducers. A standard 2-dimensional echocardiographic image was created; it depicted the tomographic anatomy traversed by the ultrasound beam in black and white. Red blood cell flow velocities directed

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toward or away from the transducer were encoded in 16 to 32 shades of red or blue, respectively, and superimposed on the appropriate location on the echocardiographic image. Green was added to the color in each pixel in proportion to the variance in the Doppler signal, and served as an indicator of nonlaminar flow. The frame rate was variable depending on depth, sector arc and number of ultrasound interrogating bursts per scan line. The maximal possible frame rate was 30 frames/s at 12 cm depth, 15° sector arc and 4 bursts/scan line. Each study was performed using the narrowest sector angle and shallowest depth that encompassed the entire jet area. The maximal discernible velocity recordable without aliasing was 64 cm/s at 12 cm depth. Optimal gain settings were used in all patients, and were defined as the maximal gain level possible without introducing background artifact (color signals outside of flow areas or carryover of color signal from an accompanying chamber).[21]

Doppler examination: CDFI examinations were performed using 5 transducer orientations to identify the regurgitant jet. The views obtained included the parasternal and apical long-axis, parasternal short-axis, 4-chamber apical and 2-chamber apical views. The optimal view for further study was chosen as the plane that most clearly displayed the largest definable regurgitant jet. This imaging plane was then maintained throughout the remainder of the study without further modification of the gain settings, frame rate or depth.

The electrocardiogram and blood pressure (by cuff sphygmomanometer) were monitored throughout the protocol, and recorded at baseline and during isometric contraction. The stress of isometric exercise was imposed using sustained handgrip of a calibrated dynamometer at one-third maximal achievable force (range 10 to 60 kg) for a minimum of 1 minute; during and immediately after this, CDFI recordings for measurements were recorded. Patients received careful instruction to avoid an associated Valsalva maneuver.

Jet measurements: All studies were stored on 1/2-inch VHS videotape for playback and analysis. Regurgitant jet area was measured from off-line videotape images at baseline and at the end of the isometric exercise. Jet area was obtained by planimetering the outer

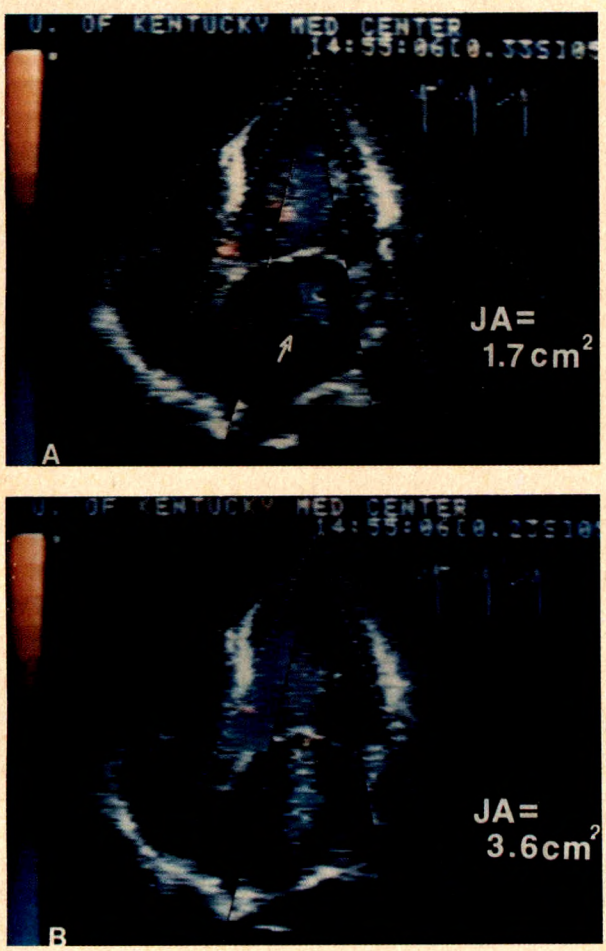


FIGURE 1. Systolic frames of mitral regurgitation before (*A*) and after (*B*) handgrip. The mitral regurgitation, depicted as a blue jet (*arrow*), is seen to increase from 1.7 to 3.6 cm². Narrow sector views have been superimposed on wide angle views for anatomic orientation. JA = jet area.

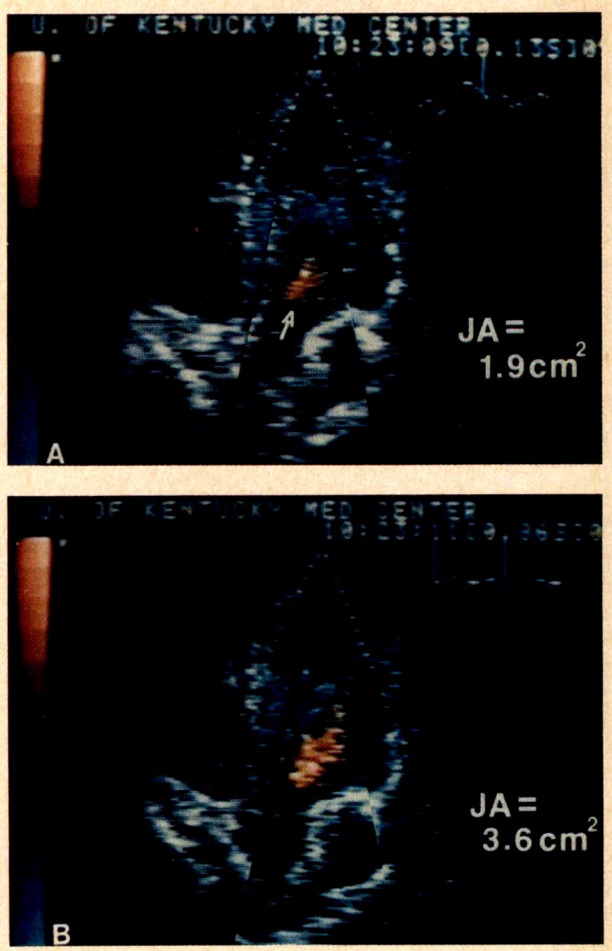


FIGURE 2. Diastolic frames of aortic regurgitation before (*A*) and after (*B*) handgrip. The aortic regurgitation, depicted as an orange jet (*arrow*), is seen to increase from 1.9 to 3.6 cm². Narrow sector views have been superimposed on wide angle views for anatomic orientation. JA = jet area.

border of the largest clearly definable flow disturbance using a digitizing pad and light pen. The traced jet area included variance signals, aliased images and contiguous nonturbulent velocities. Measurements were taken from 3 cardiac cycles and expressed as mean jet area ± standard deviation. All measurements were done by a single observer to avoid unacceptable variability from interobserver differences. We have previously demonstrated acceptable intraobserver variability necessary to allow sequential analysis of an interventional effect.[25] Detection of maximal jet area with aortic insufficiency may be complicated by merging of signals from mitral inflow. When possible, maximal aortic regurgitation jet area was measured during isovolumic relaxation before mitral valve opening. Slow frame rates did not always allow identification of a jet in this manner, in which case the largest separately defined aortic regurgitation jet was analyzed. Temporal consistency was maintained for measurements of jet area before and after handgrip in each individual patient.

Statistics: Data were analyzed before and after intervention using the Student *t* test, simple linear regression analysis and analysis of variance. The mean arterial pressure was calculated as: 2 (systolic) + (diastolic)/3.

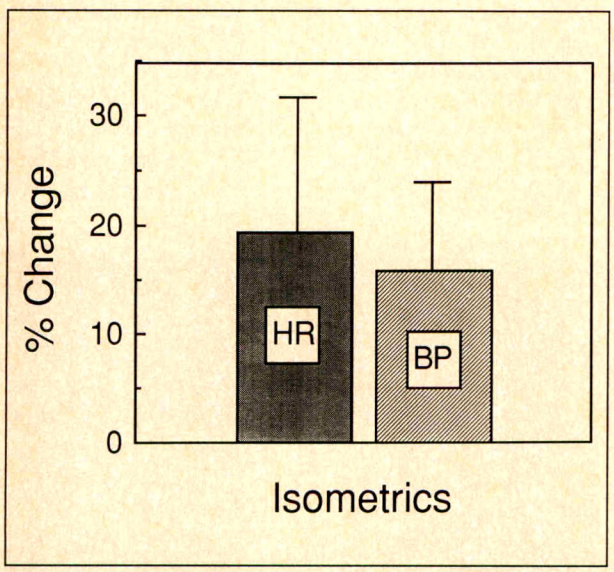


FIGURE 3. Mean percent increase in heart rate (HR) and systolic blood pressure (BP) produced with isometric exercise.

RESULTS

Study group: Technically adequate studies were obtained at rest and with isometric exertion in 34 patients. No untoward effects due to handgrip occurred, and the patients tolerated the procedure well. Data for the 16 patients receiving vasodilators or angiotensin-converting enzyme inhibitor therapy were generally similar to those of untreated patients. Therefore, we present results for the group as a whole with specific comment on those areas in which patients taking pharmacologic therapy differed. A wide spectrum of jet areas was measured from CDFI examinations (range 0.6 to 21.5 cm^2). The range of baseline jet areas was slightly greater for mitral regurgitation (0.6 to 21.5 cm^2, mean 6.2) than for aortic regurgitation (1.2 to 11.0 cm^2, mean 4.5). The mean jet area for all lesions evaluated increased significantly in response to isometric exertion from 5.4 ± 4.7 to 7.3 ± 5.2 cm^2 ($p < 0.0001$). Representative still frames are depicted in Figures 1 and 2.

Heart rate and blood pressure: Handgrip produced an increase in both heart rate and blood pressure in every patient in the study. Group mean ± standard deviation values for heart rate at rest (71.0 ± 16.4 beats/min) increased to 83.4 ± 16.7 with isometrics (p

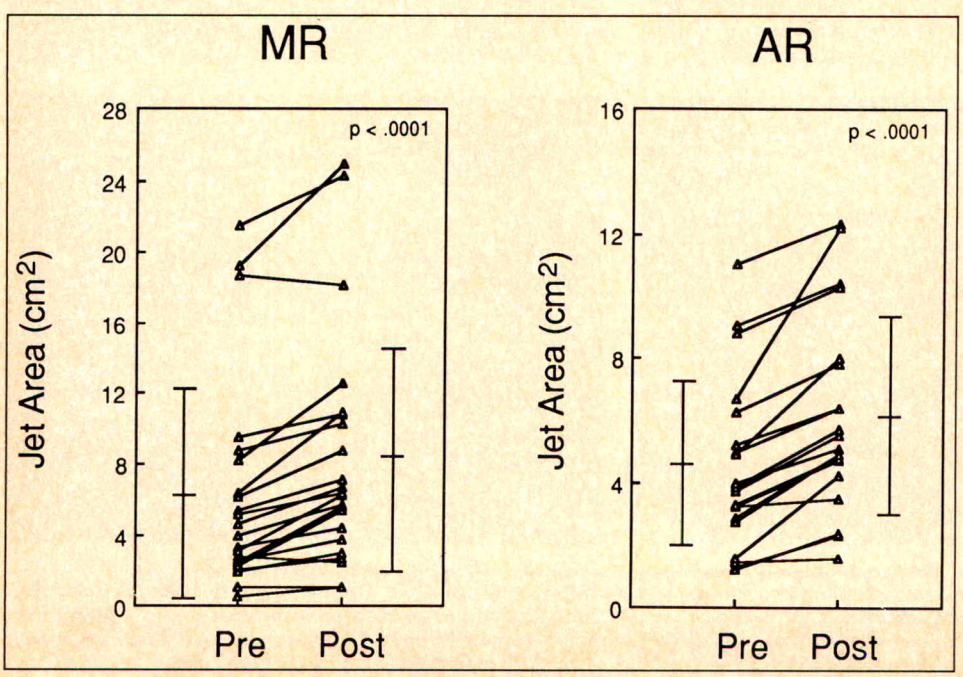


FIGURE 4. Jet areas at baseline and after handgrip for individual patients with mitral regurgitation (*left*) and aortic regurgitation (*right*).

<0.0001). Similarly, average resting blood pressure measurements for the group (132/64 mm Hg) increased to 153/70 after handgrip ($p < 0.0001$). The percent increase in heart rate for the group after handgrip was 19 ± 12%. For blood pressure it was 16 ± 7% for systolic (Figure 3), 11 ± 21% for diastolic and 14 ± 11% for mean (1/3 pulse pressure + diastolic) arterial pressure.

Mitral regurgitation: The regurgitant jet area for the patients with mitral regurgitation significantly increased in response to static exercise from 6.2 ± 5.9 to 8.2 ± 1.4 cm^2, $p < 0.001$ (Figure 4). A mean percent increase in jet area of 43% for all patients with mitral regurgitation was observed (Figure 5). A weak inverse correlation existed between baseline jet area and percent change in jet area in response to isometric maneuvers ($r = -0.41$, $p = 0.05$). However, no relation to change in absolute jet area was observed.

Aortic regurgitation: A significant increase in the mean aortic regurgitant jet area from 4.5 ± 2.7 to 6.2 ± 3.1 cm^2 ($p < 0.0001$) was produced by isometric exertion (Figure 4). Again there existed a weak inverse correlation between baseline jet area and percent change in jet area ($r = -0.51$, $p = 0.02$), but no correlation between resting jet area and absolute change in jet area. The mean percent increase of 50% in jet area with isometrics in aortic regurgitation was similar to that seen with mitral regurgitation (Figure 5).

Effects of concurrent vasodilator therapy: Although the changes in heart rate and blood pressure were slightly greater for untreated patients compared to the cohort receiving vasodilators (22 vs 15% and 17 vs 10%, respectively), these differences were not statistically significant. The presence or absence of concurrent vasodilator therapy also did not have a statistically significant effect on percent change in jet area from control to handgrip (40 vs 56% for treated and untreated patients, respectively). This lack of effect was evident for both mitral and aortic regurgitation when analyzed separately. However, a slightly closer inverse correlation existed between resting jet area and percent change produced by isometrics in the subset of untreated patients than for the group overall: $r = -0.62$ for both mitral and aortic regurgitation.

DISCUSSION

The hemodynamic effects of isometric exercise have been well defined. Healthy subjects demonstrate an increase in systolic and diastolic blood pressure, heart rate and contractility while maintaining a normal systemic vascular resistance.[1-7] Subjects with a variety of heart diseases also demonstrate an increase in cardiac output and blood pressure, but exhibit an additional increase in left ventricular end-diastolic pressure and systemic vascular resistance.[10-12,17,26] The augmented left ventricular end-diastolic pressure and systemic vascular resistance suggest variable degrees of inotropic inadequacy and partial or complete reliance on Frank-Starling mechanisms in patients with diseased cardiovascular systems.[12] Shepherd et al[5] summarized this best when they noted "it seems as if the body is determined to achieve an increase in blood pressure during isometric exercise and calls upon any combination of cardiac output and peripheral resistance to achieve this goal."

In this study, we found that isometric exercise induced a significant enlargement of the regurgitant jet area that could be quantified by CDFI in patients with either aortic or mitral regurgitation. This increase in the regurgitant jet was similar in magnitude to the change observed in blood pressure and heart rate. The magnitude of increase in the size of flow disturbance was also similar for patients with either mitral or aortic regurgitation.

CDFI provides an excellent method for the detection of valvular regurgitation. The sensitivity of CDFI has been reported to be from 86 to 94% and specificity to be 100% for the identification of various forms of regurgitation.[18,21] Early studies documented a relation between the length of regurgitant jet by color flow Doppler mapping and angiographic severity of the lesion.[18,21] More recently, studies have demonstrated the ability of the planimetered area of disturbed flow to semiquantify the magnitude of regurgitation.[20,24]

Although previous studies have shown a good correlation between CDFI and angiography, only a general correlation has been found with measures of regurgitant volume.[24] This difficulty in predicting regurgitant volume is undoubtedly related to the fact that multiple variables contribute to the ultimate size of the jet area produced by any lesion.[27,28] Variables that may affect quantitation of valvular regurgitation by CDFI include: transvalvular pressure gradient, orifice size, retrograde chamber size and compliance, and duration of gradient as influenced by heart rate.[27] Accordingly, it is possible that an increase in transvalvular pressure gradient due to isometrics may have resulted in an increased jet area secondary to augmented velocity without a proportionate change in regurgitant volume.

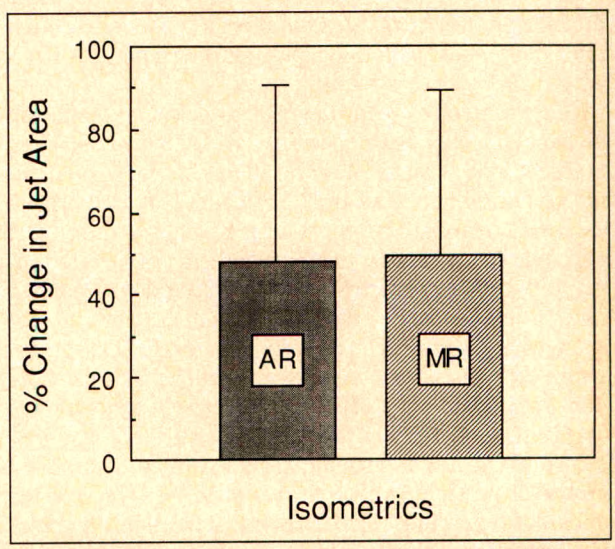


FIGURE 5. Mean percent increase in jet area produced by handgrip for aortic regurgitation (AR) and mitral regurgitation (MR).

The precise mechanism for the increase in jet area observed with CDFI after isometrics remains to be established. The magnitude of regurgitation produced by any lesion is determined by regurgitant orifice area as well as by hemodynamic factors including heart rate, contractility, preload and systemic vascular resistance.[29–33] An increase in systemic vascular resistance associated with handgrip could, of course, significantly enhance both mitral and aortic regurgitation. We believe that it is most likely that regurgitant jet area is augmented by a combination of effects on these factors, and that the individual components are not easily separated.

We examined the question of whether patients with mild or severe valvular regurgitation as manifested by small and large jet areas differed in the magnitude of response to isometrics. When the change in jet area was analyzed in terms of absolute magnitude in cm^2, no relation to the size of the disturbed flow at rest was observed. Neither was the change in jet area related to the magnitude of alteration in heart rate or blood pressure after handgrip. Thus, mitral and aortic regurgitation patients with large flow disturbances by CDFI do not appear to exhibit greater increases in jet area secondary to isometric exertion than do patients with evidence of mild regurgitation manifested by small jet areas.

The lack of effect of long-term vasodilator therapy on the changes inducible in jet area was not expected. Wilson et al[34] documented an acute decrease in wall stress secondary to nitroglycerin in patients with asymptomatic aortic regurgitation. Similar effects have been seen with other afterload reducing agents including nifedipine and nitroprusside.[31,35] While 3 individual subjects who were receiving vasodilators did exhibit a minimal response (<10% increase in jet area) to isometrics by CDFI, no statistically significant differences could be detected when compared to the entire group of patients. These observations raise questions regarding whether long-term vasodilator therapy is efficacious in modulating the hemodynamic effects of isometric exercise in patients with valvular regurgitation, and if so, what dosage level is required.

Certain factors regarding the collection and analysis of our data may have contributed to our results. First, inherent limitations of CDFI, such as attenuation of the ultrasound signal, aliasing, the effect of gain and considerations relating to maintaining stable transducer position, have been well described and apply to this study.[21,27,28] Second, measurements could not be performed in a totally nonblinded fashion, due to the changes in heart rate produced by handgrip. Third, contamination of the aortic regurgitation jet by mitral inflow may result in difficulty in precisely defining the maximal jet area. The isovolumic aortic jet visualized before mitral valve opening was used for measurement whenever possible. Although this may not represent the maximal regurgitant jet, it provides data regarding relative size.

The findings of the present study have implications for the clinical application of CDFI in the assessment of valvular regurgitation. Regardless of the precise mechanism, our data clearly demonstrate the ability of an acute intervention to produce major transient alterations in the size of regurgitant flow disturbance. Therefore, one must be cognizant of this potential when using CDFI in the clinical evaluation and semiquantitation of a patient with valvular insufficiency. Such changes may be of particular importance in interpreting the significance of changes in jet area detected on serial examinations.

Acknowledgment: We would like to thank Lynne Cornish for secretarial assistance.

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Short- and Long-Term Effects of Cigarette Smoking on Heart Rate Variability

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The short- and long-term effects of cigarette smoking on autonomic cardiac regulation were investigated by power spectral analysis of heart rate variability under controlled respiration (15/min). The short-term effects were examined in 9 smokers without evidence of cardiopulmonary disorders after an overnight abstinence from smoking. The heart rate spectral component reflecting the respiratory sinus arrhythmia (0.25 Hz), a quantitative index of vagal cardiac control, decreased 3 minutes after smoking 1 cigarette ($p = 0.0061$) and the component reflecting Mayer wave sinus arrhythmia (0.04 to 0.15 Hz), which includes sympathetically mediated activity, increased after 10 to 17 minutes ($p = 0.0124$). The long-term effects were examined in 81 normal subjects comprising 25 nonsmokers, 31 moderate (1 to 24 cigarettes/day) smokers and 25 heavy (>25 cigarettes/day) smokers after an overnight abstinence. Although the magnitude of the Mayer wave component was unaffected by the smoking status, the respiratory component in the supine position was smaller in the young (≤30 years) heavy smokers than in the young nonsmokers or moderate smokers ($p = 0.0078$). Also, postural changes in the components, a decrease in the respiratory component and an increase in the Mayer wave component with standing, were observed in the nonsmokers but not in the heavy smokers. These results suggest that smoking causes an acute and transient decrease in vagal cardiac control, and that heavy smoking causes long-term reduction in vagal cardiac control in young people and blunted postural responses in autonomic cardiac regulation.

(Am J Cardiol 1990;65:84–88)

Smoking acutely increases sympathetic activities and causes plasma catecholamine levels to increase.[1–5] This has been recognized as a major mechanism for increased risk of coronary artery disease in smokers. However, the epidemiologic finding that smokers have a lower blood pressure between cigarettes than nonsmokers[6,7] suggests that the sympathetic activities in smokers are not persistently increased. Many recent studies[8–11] have reported increased susceptibility to sudden coronary death and increased subsequent mortality after myocardial infarction in patients with decreased vagal cardiac control assessed by heart rate variability. The decrease in vagal cardiac activities may be present in smokers and may be a reason for the association between smoking and cardiac death.

In this study, we examined short- and long-term effects of smoking on autonomic cardiac control using spectral analysis of heart rate variability.[12–17] The heart rate power spectral density contains ≥2 major frequency components, which reflect the activities of different divisions of the autonomic regulation system.[12–15] The respiratory component[16] is a quantitative reflection of respiratory sinus arrhythmia,[12] and the Mayer wave component[16] (0.04 to 0.15 Hz) is derived from a blood pressure variability through the baroreflex mechanism.[12] The magnitudes of these components respectively provide a quantitative index of vagal cardiac control and an index of sympathetic cardiac control with vagal modulation.[13–15]

METHODS

Study I: Nine male volunteers, aged 24 to 30 years, with normal history, physical examination and laboratory tests, including complete blood count, blood chemistry, chest x-ray and electrocardiography, were selected from among the hospital staff and their relatives. None of them took any medication the week before the study. All were regular cigarette smokers, consuming 20 to 40 (mean 27 ± 8) cigarettes/day. On the day before the study, they were instructed to refrain from smoking, or drinking beverages containing caffeine or alcohol, for >8 hours before the study and to take a light breakfast before 8:00 A.M. The study was performed between 10:00 A.M. and 12:30 P.M. After a supine resting period of >30 minutes, the subjects smoked 4 cm of 1 cigarette containing 1.0 mg of nicotine during 2 minutes in the supine position, inhaling the cigarette smoke deeply. The autonomic function was tested before and 3, 10, 17 and 24 minutes after the start of smoking.

Study II: Eighty-one healthy male volunteers, aged 19 to 52 years, were enrolled, using the same selection

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criteria as in study I. According to the smoking status, they were divided into 3 groups: 25 nonsmokers, 31 moderate smokers (1 to 24 cigarettes/day) and 25 heavy smokers (>25 cigarettes/day). Mean habit durations in the moderate and heavy smokers were 11.6 and 12.4 years, respectively. They were instructed as in study I, and the autonomic function was tested between 10:00 A.M. and 12:30 P.M. after a supine resting period of >30 minutes without smoking.

Autonomic function test: Electrocardiogram (CM_5 lead) and respiratory waveforms (nose-tip thermistor) were continuously stored on a frequency modulated tape recorder (TEAC MR-30). Data were collected for 5 minutes in the supine position. Also, 5-minute data while standing were collected in study II. During the test the subjects breathed quietly to the metronome signal at 15 beats/min (0.25 Hz), to obtain a stationary respiratory sinus arrhythmia without frequency change or phase drift.[15–17] Blood pressure was measured at the end of the autonomic function tests in each position.

Data analysis: The electrocardiogram was digitized at 1,000 samples/s/channel with a Canopus Electronics A/D converter (ADX-98E), and all RR intervals were measured with a fast peak detection algorithm at an accuracy of 1 ms on an NEC microcomputer (PC-9801VX). Only the time series comprising 250 to 300 normal sinus RR intervals during which the subjects faithfully matched all breaths to the metronome were included in the final analysis.

We calculated the power spectral density of RR interval variability by an autoregressive algorithm that computed the autoregressive coefficients by the Marple method.[18] The model order was chosen as the one that minimized Akaike's final prediction error figure of merit.[19] The program computed individual power and center frequency of each spectral component (Figure 1).[20] We defined the components at 0.04 to 0.15 Hz as the Mayer wave[21] component and those at the respiration frequency (0.25 Hz) as the respiratory component. In considering the RR interval variation attributable to each single component, we represented the magnitudes of individual components by the parameter we termed the coefficient of component variance, which is calculated as 100 · (power of a component)$^{1/2}$/(mean RR interval) (%).[15,16]

Statistical analysis: We used 2-way (time after smoking and subject) analysis of variance followed by the Bonferroni test to compare data after smoking with the control value in study I. We compared the spectral variables among the 3 groups in study II after adjusting for the effect of age using analysis of covariance for general linear models (least square means method) by means of the Statistical Analysis System. We used Student *t* tests for paired samples to evaluate the effects of posture. A p value <0.05 was considered significant.

RESULTS

Study I: The mean RR interval decreased after smoking 1 cigarette ($p < 0.0001$) (Figure 2). Systolic and diastolic blood pressures increased after smoking, but the changes were not significant. The magnitude of the Mayer wave component began to increase 10 minutes after the start of smoking, remained at a high level after 17 minutes and returned to the control level by 24 minutes ($p = 0.0124$). The magnitude of the respiratory component decreased after 3 minutes, and returned to the control level by 10 minutes ($p = 0.0061$).

Study II: The magnitudes of heart rate spectral components have been known to decline with age.[14–17] In an earlier study[17] and in our previous study[16] the rate of

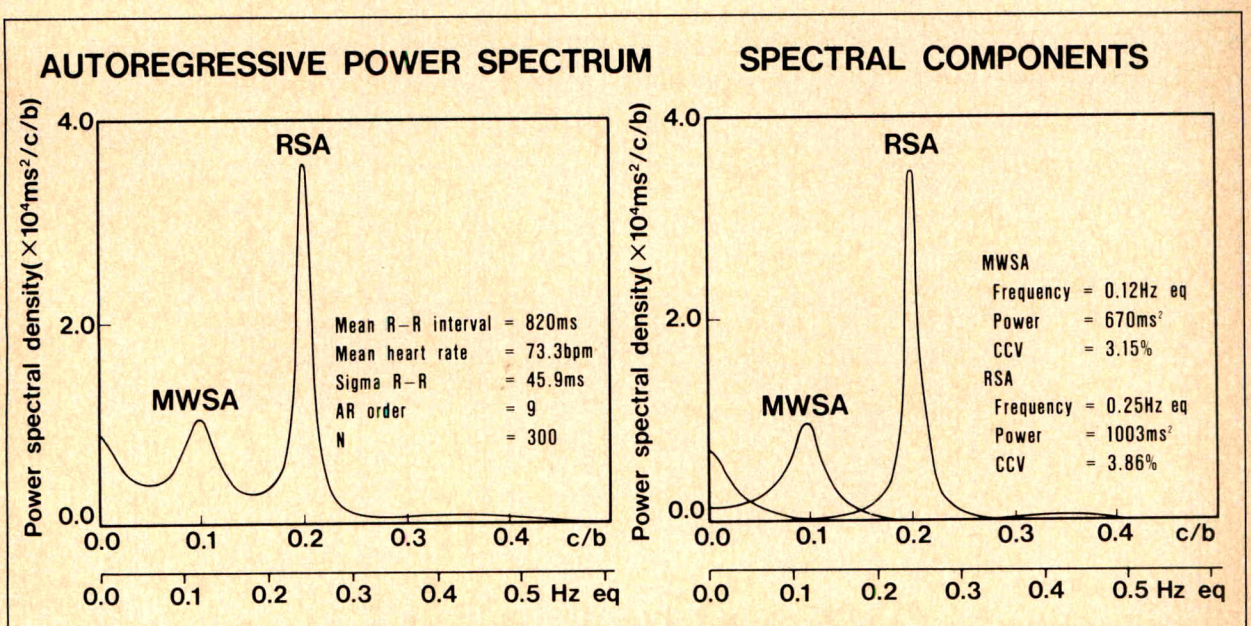


FIGURE 1. Representative example of autoregressive spectral analysis of RR interval variability in healthy subject. The power spectral density (*left*) contains 2 major components reflecting the respiratory sinus arrhythmia and Mayer wave sinus arrhythmia. Power, coefficient of component variance and center frequency of these components are calculated by spectral component analysis (*right*). AR = autoregressive; CCV = coefficient of component variance (see text); c/b = cycle/beat; Hz eq = Hz equivalent; MWSA = Mayer wave sinus arrhythmia; RSA = respiratory sinus arrhythmia.

TABLE I Basic Hemodynamic Parameters After Abstinence from Smoking

	Nonsmokers	Moderate Smokers (1–24/day)	Heavy Smokers (>25/day)
≤30 years (n)	15	13	11
Age (yrs)	24 ± 3	25 ± 3	26 ± 3
Supine			
RR interval (ms)	1,015 ± 154	937 ± 132	885 ± 139
Systolic BP (mm Hg)	114 ± 9	118 ± 8	118 ± 8
Diastolic BP (mm Hg)	68 ± 8	67 ± 7	72 ± 7
Standing			
RR interval (ms)	777 ± 86*	756 ± 68*	747 ± 96*
Systolic BP (mm Hg)	111 ± 10	119 ± 9	116 ± 7
Diastolic BP (mm Hg)	83 ± 8*	82 ± 10*	85 ± 6*
>30 years (n)	10	18	14
Age (yrs)	39 ± 6	40 ± 6	37 ± 5
Supine			
RR interval (ms)	878 ± 118	918 ± 109	875 ± 150
Systolic BP (mm Hg)	116 ± 5	117 ± 11	115 ± 10
Diastolic BP (mm Hg)	73 ± 8	76 ± 9	70 ± 9
Standing			
RR interval (ms)	756 ± 94*	770 ± 97*	740 ± 130*
Systolic BP (mm Hg)	116 ± 6	113 ± 10	112 ± 9
Diastolic BP (mm Hg)	84 ± 7*	84 ± 8*	79 ± 9*

* $p < 0.01$ vs supine position. Values are mean ± standard deviation.
BP = blood pressure.

the decline has been shown to be greatly reduced after 30 years. Thus, the subjects in study II were divided into 2 groups by age: ≤30 years and >30 years (Table I).

Although the magnitude of the Mayer wave component was unaffected by the smoking status in either age group, it increased with standing only in the young (≤30 years old) nonsmokers ($p < 0.05$), but not in the moderate or heavy smokers (Figure 3). On the other hand, the magnitude of the respiratory component in the young subjects was significantly lower in the heavy smokers than in the nonsmokers and moderate smokers ($p = 0.0078$), but no difference was found in the older subjects (>30 years old). In both age groups, the magnitude of the respiratory component decreased with standing in the nonsmokers and moderate smokers ($p < 0.01$ for all comparisons), but not in the heavy smokers.

DISCUSSION

We found that cigarette smoking causes acute and transient changes in the heart rate spectral components, and that even after an overnight abstinence the supine respiratory component in the subjects ≤30 years of age is decreased in the heavy smokers. Also, the postural responses of the components were blunted over the long term in the heavy smokers. These results suggest that smoking causes not only short- but also long-term alterations in autonomic cardiac control.

Spectral components of heart rate variability: The magnitude of the respiratory component has been accepted as an index of vagal cardiac control.[13,17] Intravenous atropine abolishes this component, but propranolol has no effect on it.[12,13] Moreover, a recent study[22] on the transfer function of autonomic regulation showed that the heart rate fluctuation at the usual respiration frequency (0.15–0.5 Hz) is only vagally but not sympathetically mediated. Also, we have previously reported that the coefficient of component variance for the respiratory component correlates linearly with the vagal cardiac control defined as $(HR_{P+A} - HR_P)/HR_{P+A}$, where HR_P is the heart rate after propranolol (0.2 mg/kg) and HR_{P+A} is that after additional atropine (0.04 mg/kg).[15]

Although the respiratory component shows a decrease while standing, the Mayer wave component shows a β-adrenergically mediated increase.[13–17] The Mayer wave component is thought to be derived from the fluctuation in the vasomotor activity at about 0.1 Hz through the baroreflex mechanism,[12] in which the cardiac efferent is both vagally and sympathetically mediated.

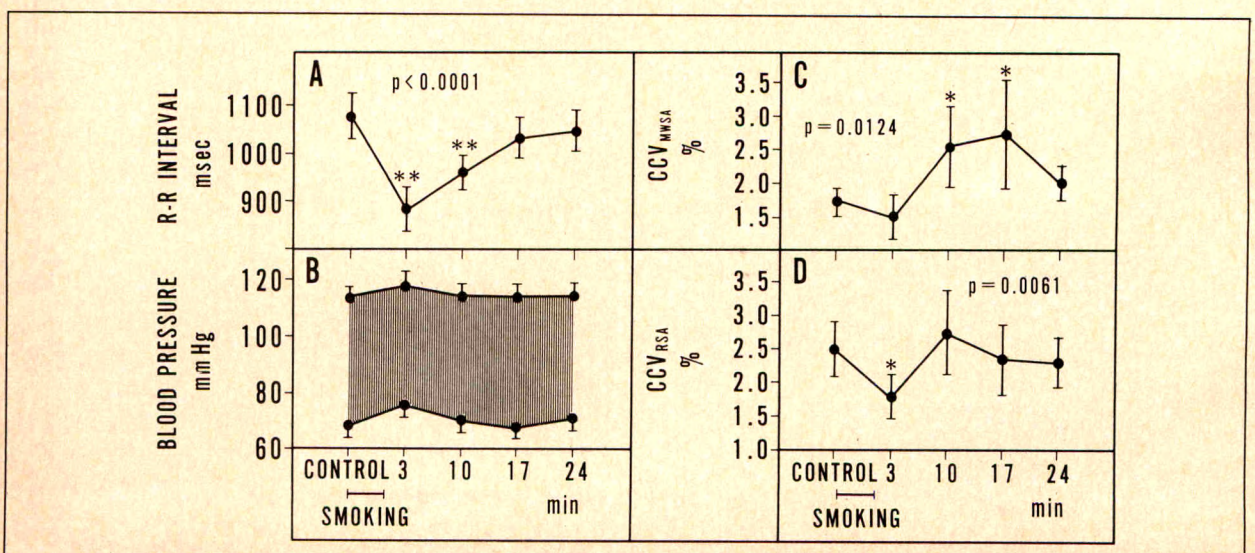


FIGURE 2. The short-term effects of cigarette smoking on RR interval (*A*), blood pressures (*B*), CCV_{MWSA} (*C*) and CCV_{RSA} (*D*). *Error bars* denote standard error of the mean. Abbreviations as in Figure 1.

Short-term effects of smoking: Most of the acute effects of smoking on neurocardiovascular regulation can be explained as the effects of nicotine.[5] The mechanisms of the effects of nicotine include both stimulation and blocking of the autonomic ganglia, direct liberation of catecholamine stores in the heart, liberation of adrenomedullary epinephrine, stimulation of carotid body chemoreceptors and aortic baroreceptors and direct action in the central nervous system.[3,4,23–25]

Our observation of the transient decrease in the respiratory component after 3 minutes of smoking suggests that smoking acutely suppresses vagal cardiac control. Nadeau and James[24] have shown that, although the direct perfusion of nicotine (10 μg) to the sinoatrial node in the dog causes a cholinergically mediated brief slowing of the heart within the initial 10 seconds, it also causes a nonreaction of the heart to electrical stimulations of the cervical vagus for >5 minutes. The latter corresponds to the ganglionic blocking effect of nicotine, and our observation may indicate that this effect of nicotine is manifested even by cigarette smoking in humans.

The short-term increase in the Mayer wave component with smoking may be the result of either or both liberation of catecholamines or stimulation of baroreceptors. It is well established that plasma catecholamine levels increase within 1 minute after smoking or an infusion of nicotine.[1,2] Although absence of the increase in the Mayer wave component after 3 minutes of smoking appears inconsistent with the reported changes in plasma catecholamine levels, this may be attributable to the concomitant decrease in vagal cardiac control at this time. The increase in this component after 17 minutes, on the other hand, can be explained as the result of the stimulation of baroreceptors rather than the liberation of catecholamines, because the RR interval and blood pressures at this time had already returned to the control levels (Figure 2).

Long-term effects of smoking: Our observation of long-term reduction in the supine respiratory component in the young heavy smokers suggests that heavy smoking causes long-term reduction in vagal cardiac control in young people. This finding is consistent with the epidemiologic findings that smokers, between cigarettes, show a higher heart rate than nonsmokers.[6,7]

The absence of postural changes in the heart rate spectral components in heavy smokers suggests that heavy smoking causes blunted postural responses in autonomic cardiac regulation. Despite the fact that smoking acutely increases blood pressure,[4] the blood pressure in long-term smokers, between cigarettes, is less than the average blood pressure in nonsmokers.[6,7] In most epidemiologic studies blood pressure is measured in the sitting position,[7] such that the blunted postural responses may contribute to a decrease in blood pressure in this position.

We cannot explain the mechanism for the long-term alterations in autonomic function in heavy smokers. Smoking possibly has an effect on various parts in the neurocardiovascular regulation system, which includes the heart, lung, blood vessels, the afferent and efferent division of the autonomic nervous system and the cen-

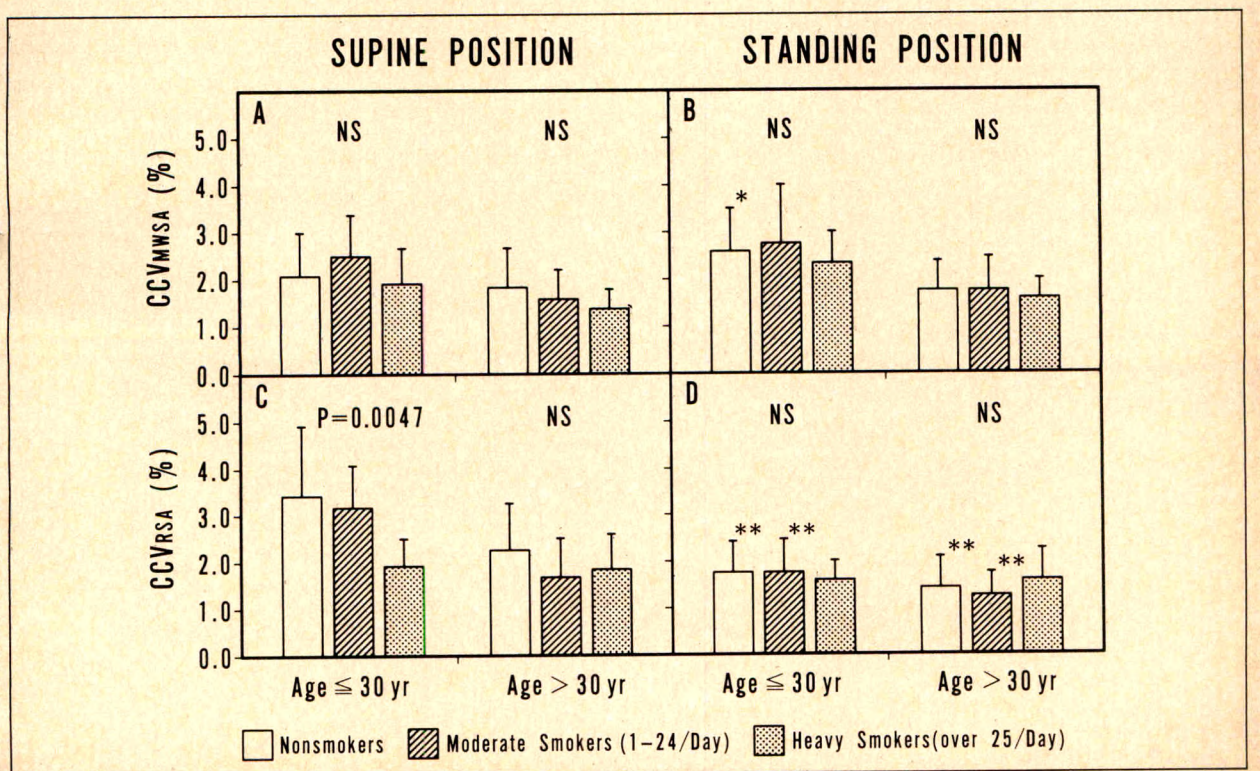


FIGURE 3. The effects of smoking status on the supine and standing CCV values after an overnight abstinence from smoking. Data are least square means adjusted for the effect of age, and *error bars* denote standard errors of the least square mean. *p <0.05, **p <0.01; values significantly differ from those in the supine position. Abbreviations as in Figure 1.

tral nervous system.[3,23] Also, the differences in other factors, such as exercise level, between smokers and nonsmokers may be related to our results. Further studies (including animal investigations) are required to establish the pathogenesis of our findings.

Clinical implications: Population studies[26–28] have shown an increased rate of cardiac death in cigarette smokers, and several mechanisms have been known to contribute to the association between smoking and cardiac death.[3,4] Our findings of short- and long-term reduction in vagal cardiac control may add 1 more mechanism to this association, because many recent studies have shown that patients with decreased vagal cardiac control assessed by heart rate variability have increased susceptibility to sudden coronary death,[8] increased subsequent mortality after acute myocardial infarction[9] or increased late mortality after coronary angiography.[10]

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Pressor Effect of Inhaled Ergotamine in Orthostatic Hypotension

Italo Biaggioni, MD, Deborah Zygmunt, MD, Virginia Haile, RN, and David Robertson, MD

Treatment of orthostatic hypotension due to autonomic failure frequently necessitates use of pressor agents. Because venous pooling contributes significantly to this disorder, the venoconstrictive properties of ergotamine offer theoretical advantages over pure arteriolar pressor agents. However, the low and erratic bioavailability of oral preparations has hindered the use of ergotamine. Accordingly, the efficacy of inhaled ergotamine tartrate (1 puff, 0.36 mg) was compared to placebo in 8 patients with severe autonomic failure. Blood pressure was monitored in the seated position with an automated device. Ergotamine produced significant increases in systolic (29 ± 5 mm Hg, $p < 0.01$ by analysis of variance) and diastolic (13 ± 1 mm Hg, $p < 0.001$) blood pressures compared to placebo (−9 ± 5 and −2 ± 3, respectively). Upright blood pressure 2 hours after administration was significantly greater with ergotamine (119 ± 8/69 ± 6 mm Hg) vs placebo (82 ± 7/59 ± 5 mm Hg, $p < 0.05$). Motionless standing time, a measurement of functional capacity, also improved with ergotamine (200 ± 58 vs 85 ± 22 seconds). No side effects were noted, but patients with coronary or peripheral artery disease were excluded. Inhaled ergotamine may provide an effective and practical therapy for disabling orthostatic hypotension due to autonomic failure.

(Am J Cardiol 1990;65:89–92)

Orthostatic hypotension due to autonomic failure can be severely disabling. Initial therapy for this disorder includes increased salt intake, fitted stockings and mineralocorticoids.[1,2] However, addition of pressor agents is generally required in severely affected patients to provide adequate symptomatic relief. One such drug is ergotamine, which has been reported to preferentially improve upright blood pressure in patients with orthostatic hypotension.[3] However, use of ergotamine has been hampered by the low and erratic bioavailability of oral and sublingual preparations.[4,5] Long-term use of parenteral preparations, although effective, is limited by practical considerations. An inhaled ergotamine preparation has been found to be efficacious for the treatment of migraine. This prompted us to test the pressor effects of inhaled ergotamine in patients with severe orthostatic hypotension due to autonomic failure. A case report using this approach has recently been described.[6]

METHODS

Eight patients with moderate to severe autonomic failure were admitted to Vanderbilt University's clinical research center. Patients abstained from methylxanthine-containing beverages and all medications and were placed on a diet containing 150 mEq of sodium and 60 mEq of potassium/day for at least 3 days before the study. Autonomic function was evaluated as previously described.[7] Five patients were diagnosed as having multiple system atrophy (Shy-Drager syndrome) due to the presence of autonomic failure in association with other central neurologic abnormalities. Three patients had isolated autonomic failure, absence of central neurologic abnormalities and absence of secondary causes of autonomic failure, and were diagnosed as having primary autonomic failure (idiopathic orthostatic hypotension). Patients were excluded from the study if they had a history or clinical symptoms consistent with myocardial or peripheral artery disease.

All studies were performed with the patients seated and fasting. Blood pressure and heart rate were recorded automatically every 3 minutes with an oscillometric blood pressure monitor (Dinamap, Critikon Inc.) to avoid observer bias. Values were averaged to the corresponding 15-minute periods. On different days, and after a 30-minute baseline period, patients received either placebo inhaler or ergotamine tartrate inhaler (Ergotamine Medihaler, Riker Laboratories, 1 puff, 0.36 mg), in a single-blind, crossover fashion. Blood pressure and heart rate were measured for an additional 120 minutes. At the end of this period, upright blood pressure and "motionless standing time" (the time the patients could remain standing motionless before symptoms of ortho-

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TABLE I Clinical Characteristics

Pt No.	Age (yrs), Sex	Diagnosis	Blood Pressure (mm Hg) Supine	Blood Pressure (mm Hg) Upright	Heart Rate (beats/min) Supine	Heart Rate (beats/min) Upright	Plasma NE (pg/ml) Supine	Plasma NE (pg/ml) Upright	Maximal Response* (mm Hg)
1	54, M	MSA	124/95	64/50	68	80	353	296	25
2	67, F	MSA	152/92	48/—	76	81	138	195	37
3	68, F	MSA	164/92	60/40	80	80	272	231	26
4	66, F	PAF	133/85	80/55	64	68	44	86	23
5	70, M	MSA	141/88	84/66	60	72	132	178	34
6	71, M	MSA	162/89	121/80	60	68	184	269	48
7	76, F	PAF	156/88	110/68	64	70	137	348	9
8	66, F	PAF	181/106	80/51	64	70	126	284	38
Mean	67		152/92	81/59	67	74	173	236	30
± SEM	±2		±6/±2	±9/±5	±2	±2	±32	±27	±4

* Maximal increase in systolic blood pressure after inhaled ergotamine 0.36 mg.
NE = norepinephrine; PAF = primary autonomic failure; MSA = multiple system atrophy; — = undetectable.

static hypotension developed) were measured in 7 patients. This time point was chosen because preliminary studies showed that the effects of ergotamine were near maximal at 2 hours. Blood pressure was not measured in the supine position because patients with severe autonomic failure commonly have baseline supine hypertension (Table I).

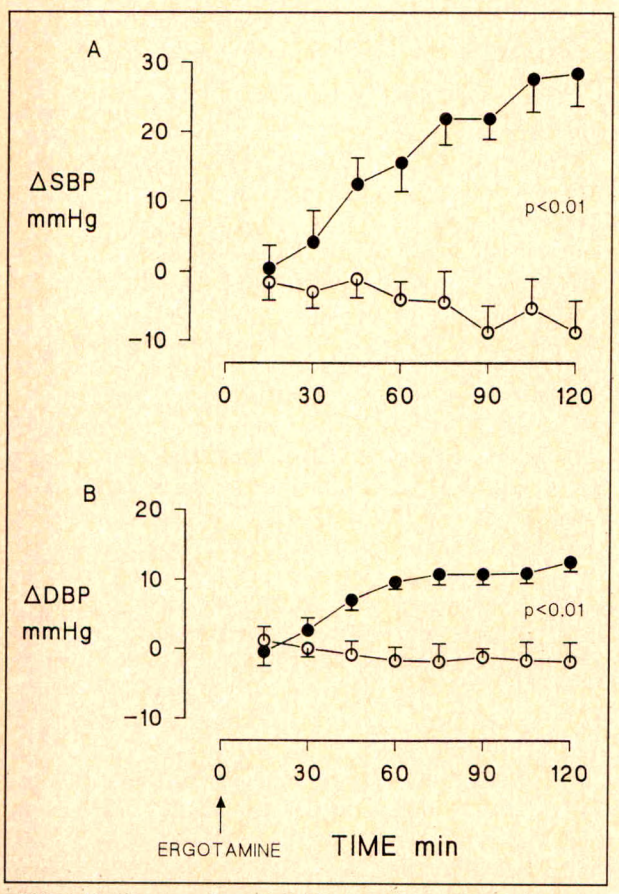


FIGURE 1. Changes in seated (*A*) systolic and (*B*) diastolic blood pressure (BP) in 8 patients with severe autonomic failure after oral administration of placebo (*open circles*) or ergotamine, 0.36 mg, (*filled-in circles*) given by inhalation. Changes were significant for systolic (p <0.01) and diastolic blood pressure (p <0.001) by analysis of variance. *Vertical lines* indicate mean ± standard error of the mean. D = diastolic; S = systolic.

Results are presented as mean ± standard error of the mean. Statistical comparisons were made by 2-factor analysis of variance with repeated measures, using the Number Cruncher Statistical System software (NCSS). Factor A was the treatment given (placebo or ergotamine, fixed, 2 levels), and factor B was the different time periods (fixed, repeated measures, 8 levels). Differences between groups were analyzed by 2-tailed, unpaired *t* tests when appropriate. Criterion for significance was $p < 0.05$.

RESULTS

All patients had autonomic failure characterized by severe orthostatic hypotension, abnormal autonomic reflexes and an abnormal norepinephrine response to upright posture. Systolic blood pressure decreased from 152 ± 6 to 81 ± 9 mm Hg on assuming the upright posture (Table I). Adequate compensatory heart rate increase to this decrease in blood pressure was absent. Plasma norepinephrine was 173 ± 32 pg/ml in the supine position (for this age group, normal is 378 ± 5 pg/ml) and 236 ± 26 pg/ml in the upright position. This is

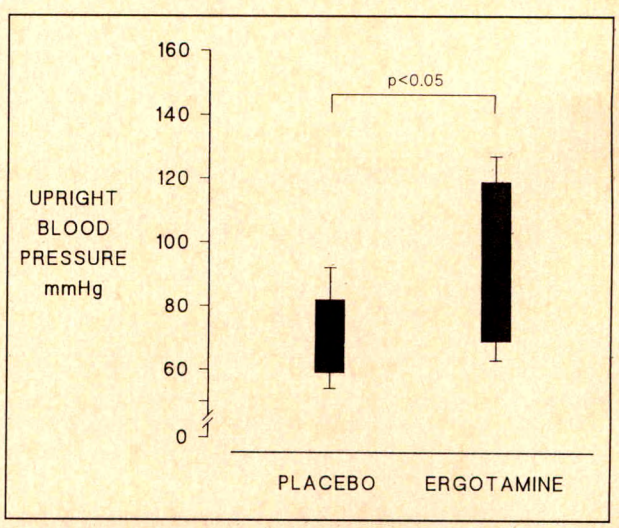


FIGURE 2. Upright blood pressure 2 hours after administration of either placebo or inhaled ergotamine. There was a significant difference in upright systolic blood pressure between treatments by unpaired 2-tailed *t* test.

clearly an abnormal response, especially considering the magnitude of orthostatic hypotension.

Placebo had no significant effect on blood pressure or heart rate (Figure 1). In contrast, 0.36 mg of inhaled ergotamine produced significant increases in both systolic and diastolic blood pressure (Figure 1). Two hours after administration, ergotamine increased systolic blood pressure by 29 ± 5 mm Hg ($p < 0.01$ by analysis of variance) and increased diastolic blood pressure by 13 ± 1 mm Hg ($p < 0.001$). Individual maximal responses are shown in Table I. Mean maximal increase in systolic blood pressure was 30 ± 4 mm Hg (range 9 to 48). Two hours after placebo administration, blood pressure decreased from 128 ± 6/73 ± 3 in the seated position to 82 ± 9/56 ± 6 mm Hg on assuming the upright posture (orthostatic change −46 ± 8/−18 ± 6 mm Hg, n = 7). By comparison, after ergotamine administration, blood pressure decreased from 141 ± 10/80 ± 4 in the seated position to 119 ± 8/69 ± 5 mm Hg on assuming the upright posture (orthostatic change −22 ± 9/−11 ± 7 mm Hg, n = 7) (Figure 2, $p < 0.05$ vs placebo for systolic blood pressure). Ergotamine also improved motionless standing time (200 ± 58 vs 85 ± 22 seconds after placebo). No side effects were noted, except mild nausea 60 minutes after ergotamine administration in patient 5.

DISCUSSION

Maintenance of the upright blood pressure requires reflex sympathetic activation to compensate for gravity-induced blood pooling and reduced venous return. When such reflex mechanisms fail, as occurs in autonomic failure, orthostatic hypotension develops. Although orthostatic hypotension is but one of the several autonomic abnormalities seen in this disorder, it is the most disabling. On the other hand, it is perhaps the symptom most amenable to treatment. Although simple measures such as increased sodium intake and fludrocortisone remain the cornerstone of treatment, the addition of pressor agents is usually required in most patients with significant orthostatic hypotension.

Previous studies have assessed the efficacy of ergotamine in the treatment of orthostatic hypotension.[3–6,8–11] Interest in this agent arises from its venoconstrictive actions.[3] Parenteral ergotamine preparations have been uniformly effective, including intramuscular, 0.5 to 1 mg,[10] or subcutaneous, 6.5 to 13 μg/kg, dihydroergotamine,[11] and intravenous ergotamine tartrate, 0.25 to 0.5 mg.[3] Oral ergotamine tartrate, 2 to 6 mg/day, was found to be effective in 4 patients with orthostatic hypotension.[3] However, oral dihydroergotamine, 5 to 20 mg/day, was ineffective in 10 patients.[10] These differences may be due to the low bioavailability of dihydroergotamine.[4,5]

Our results indicate that inhaled ergotamine tartrate is an effective pressor agent in patients with severe orthostatic hypotension due to autonomic failure. Significant increases in blood pressure were seen with doses that are 5- to 10-fold lower than those of oral ergotamine tartrate, previously reported to be effective in similar patients. Whether this represents greater bioavailability of ergotamine by inhalation remains uncertain.[12] Caffeine has also been used in combination with subcutaneous dihydroergotamine in the treatment of orthostatic hypotension, to prevent the depressor effects of meals,[11] which are prevalent in these patients.[13] Caffeine reportedly increases the absorption of dihydroergotamine[14] and these drugs are widely used in combination in several migraine preparations.

We did not determine supine blood pressures for reasons of safety. Some studies suggest that ergotamine does not increase supine blood pressure as much as it increases upright blood pressure.[3,9] However, this is not a universal finding.[11] Even in the absence of therapy, a significant proportion of patients with autonomic impairment develop supine hypertension in addition to orthostatic hypotension, as did 4 patients in the present study. Therefore, care should be taken to avoid worsening of supine hypertension by ergotamine. As a general rule, we alert our patients to avoid the supine position for 4 to 5 hours after taking any short-acting pressor agent, including inhaled ergotamine.

Long-term treatment with oral ergotamine tartrate[3] or subcutaneous dihydroergotamine[11] has been effective in the treatment of orthostatic hypotension due to autonomic failure. Our experience with long-term use of inhaled ergotamine is limited and uncontrolled. We instruct our patients to use the drug before stressful activities and usually no more than 0.36 mg (1 puff) 2 or 3 times daily. None of the patients reported herein had clinical evidence of coronary or peripheral artery disease. Patients with primary autonomic failure usually have normal myocardial function.[15] However, ergotamine has been occasionally associated with angina pectoris and sudden death in the absence of significant coronary atherosclerosis in patients with migraine.[16] There is also a recent report of a patient who had a myocardial infarction while receiving treatment with inhaled ergotamine for orthostatic hypotension.[6] Although the investigators emphasized that a causal relation in this case was far from clear, care should be taken to avoid the use of ergotamine in patients with underlying vascular disease and to caution patients against overzealous inhaler use.

Acknowledgment: We would like to thank Ronald Wiley, MD, for help in the evaluation and care of our patients, Dorothea Boemer for secretarial assistance and Bolton Smith for preparing the reference section.

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Aerobic Exercise Reduces Levels of Cardiovascular and Sympathoadrenal Responses to Mental Stress in Subjects Without Prior Evidence of Myocardial Ischemia

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Thirty-seven healthy type A men (mean age 42 years) were randomly assigned to either an aerobic exercise training group or to a strength and flexibility training group. Before exercise, subjects underwent comprehensive physiologic and behavioral assessments, including graded exercise treadmill testing with direct measurement of oxygen consumption ($\dot{V}O_2$) and measurement of cardiovascular (heart rate, systolic and diastolic blood pressure and rate pressure product) and neuroendocrine (epinephrine and norepinephrine) responses to mental arithmetic. The aerobic exercise consisted of walking and jogging at an intensity of ≥70% maximal heart rate reserve for 1 hour 3 times/week for 12 consecutive weeks. The strength training consisted of 1 hour of circuit Nautilus training 2 times/week for 12 weeks. At the completion of the exercise program, all subjects underwent repeat testing. For the aerobic group, peak $\dot{V}O_2$ increased significantly from 33.6 to 38.4 ml/kg/min ($p < 0.001$), whereas the strength group only achieved a slight increase from 34.5 to 35.6 ml/kg/min (difference not significant). During the mental arithmetic, the aerobic group experienced a greater reduction in levels of heart rate, diastolic blood pressure and rate pressure product than the strength group (after completing the exercise training programs). The aerobic group also tended to secrete less epinephrine and to show a faster recovery than the strength group after the exercise program. In addition, the aerobic group tended to exhibit less cardiovascular reactivity to mental stress after exercise training. These data suggest that aerobic exercise reduces levels of cardiovascular and sympathoadrenal responses during and after mental stress.

(Am J Cardiol 1990;65:93–98)

Epidemiologic studies have shown that high levels of habitual physical activity are associated with lowered risk of coronary artery disease.[1–3] Laboratory studies also have shown that aerobic exercise training is associated with a reduction in standard risk factors, such as lower blood pressure and a more favorable lipid profile.[4–6] Excessive activation of the sympathetic nervous system also has been implicated as a potential risk factor that may be modified with exercise. For example, studies have shown that greater cardiovascular responses to behavioral stressors are associated prospectively with increased risk for coronary artery disease and hypertension.[7–9]

Although numerous studies have shown that physically fit individuals exhibit attenuated cardiovascular responses to stress,[10] the methodologic limitations of cross-sectional studies preclude any definitive conclusion about the role of exercise training in reducing stress responses.[11] The few longitudinal studies conducted to date have reported either minimal[12,13] or no changes.[14] One exception was a study from our laboratory that reported a reduction in heart rate and blood pressure responses to a standard behavioral challenge.[15] For the present study, we attempted to replicate and extend previous findings by including measures of sympathoadrenal and cardiovascular responses to a mental stressor. Because individuals who display the type A behavior pattern have been shown to be more likely to display enhanced sympathetic responsivity,[9] only healthy type A individuals were selected to participate in this randomized clinical study.

METHODS

Subjects: Thirty-seven men who were initially rated as type A by the type A structured interview served as

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TABLE I Changes in Cardiorespiratory Performance

	Aerobic Exercise		Strength Training	
	Time 1	Time 2	Time 1	Time 2
HR at rest (beats/min)	76 ± 13	65* ± 8	71 ± 8	72 ± 10
HR at 5 METs (beats/min)	121 ± 13	108* ± 10	120 ± 14	112† ± 15
Total treadmill time (minutes)	12.2 ± 0.9	14.0* ± 1.3	12.7 ± 2.0	13.0 ± 2.0
Peak $\dot{V}O_2$ (ml/kg/min)	33.6 ± 3.0	38.4* ± 3.9	34.5 ± 4.9	35.6 ± 15.5

Mean ± standard deviation cardiorespiratory measures at time 1 and time 2 for aerobic exercise and strength training groups.
* $p < 0.0001$; † $p < 0.001$; all comparisons are between time 1 and time 2 within each group.
HR = heart rate; $\dot{V}O_2$ = oxygen consumption.

subjects for this study. All subjects were judged to be free of hypertension and clinically manifest coronary disease by medical history, physical examination and graded exercise treadmill testing. All subjects were employed full time and had at least a high school education. Ages ranged from 30 to 52 years (mean 42.3).

Exercise training: Subjects were randomly assigned to 1 of 2 exercise programs. One group (20) participated in aerobic exercise 3 times/week for 12 consecutive weeks. These sessions consisted of 15 minutes of warm-up exercises, including stretching and light biking on a stationary bicycle (<1 kp/min), followed by 35 minutes of continuous walking and jogging on a 400-meter outdoor track at an intensity of ≥70% of subjects' initial peak oxygen consumption ($\dot{V}O_2$) determined by an initial treadmill test. The other group (17) participated in strength training twice a week. Strength and flexibility training exercises consisted of 20 minutes of flexibility exercises followed by 30 minutes of circuit Nautilus training. Subjects in the strength group were encouraged not to engage in any aerobic exercise throughout the duration of the study.

All subjects underwent comprehensive physiologic and behavioral assessments before beginning the exercise program and again after the completion of the 12-week exercise program. Our focus is on the cardiovascular and neurohumoral adjustments to the mental stress testing in which subjects participated in a challenging mental arithmetic protocol.

Mental arithmetic testing: All subjects were tested individually in a sound-attenuated, temperature controlled (80°F) chamber. An indwelling venous needle was inserted 45 minutes before the initial baseline period and the subject was asked to sit quietly to permit hormonal responses to the stress of venipuncture to subside. After a 45-minute calibration period, a 15-minute baseline period was used for collection of baseline cardiovascular and catecholamine data. Heart rate and blood pressure were monitored at 1-minute intervals using a Dinamap monitor 845 (Critikon). Continuous venous blood samples were obtained using a Cormed blood withdrawal system at a rate of 0.7 cc/min. After the baseline period, subjects completed a series of serial additions for 15 minutes. Subjects first added the digits of a 3-digit number (e.g., 111 = 1 + 1 + 1 = 3), to the original number (e.g., 111 + 3 = 114) to form a new 3-digit number. This procedure was repeated for 15 minutes. At 2.5-minute intervals subjects were encouraged to "go a little faster," and were given 1-minute rest periods at 5 minutes and 10 minutes into the task. A 15-minute recovery period concluded each testing session. Blood samples were spun down and plasma frozen at −40°C until subsequent assay. Catecholamines were assayed by high performance liquid chromatography.[16,17] Subjects were tested at the same time each afternoon and were asked to refrain from coffee, tea, cola, exercise and cigarettes during the 24 hours before the procedure.

Exercise treadmill testing: On a separate day, all subjects underwent treadmill exercise testing using a protocol developed previously in our laboratory.[18] In brief, graded exercise treadmill testing began at 2.0 miles/hour and 0% grade; speed and grade were systematically increased at 1 MET/min. Subjects exercised until exhaustion during continuous electrocardiographic monitoring. Heart rate was obtained using a Hewlett Packard 4685-A digital cardiotachometer. Expired air was collected by a facemask for quantification of oxygen consumption, expired ventilation and respiratory exchange ratio at 15-second intervals with the use of an MMC Horizon System 2 Beckman metabolic measurement cart. The identical protocol was used for retesting subjects after 12 weeks of exercise participation.

Data analysis: Physiologic data were analyzed by a 2 (group) × 2 (time) repeated measures multivariate analysis of variance. Group (aerobic exercise or strength training) served as a between-subjects variable and time (before and after 12 weeks of exercise training) served as a within-subjects variable. To assess psychophysiologic stress responses, a 2 (group) × 2 (time) × 3 (baseline, task and recovery phases of the mental arithmetic test) repeated measures multivariate analysis of variance was performed for the cardiovascular (heart rate, blood pressure and rate-pressure product) measures, followed by an analysis of covariance, with resting values for each testing session serving as covariates. The catecholamine data (epinephrine and norepinephrine) were analyzed by analysis of covariance. Mean values for each phase served as the dependent variables. To assess reactivity, change scores were calculated based on the difference between mean values at baseline and during the mental arithmetic test. These data were then analyzed by analysis of covariance, with initial baseline levels serving as the covariate.

RESULTS

Thirty-five of the initial cohort of 37 subjects (95%) completed the 12-week exercise program. Two subjects dropped out of the strength group whereas no subjects dropped out of the aerobic group. (One aerobic subject experienced atrial fibrillation during his time 2 treadmill; his data were incomplete.) Compliance was excellent. Aerobic subjects attended an average of 34.9 sessions (range 28 to 39) and were at or above their training range 89% of the time. One half of the subjects

TABLE II Reactivity to Mental Arithmetic

	Aerobic Exercise		Strength Training	
	Time 1	Time 2	Time 1	Time 2
SBP (mm Hg)	15 ± 7	11 ± 6†	20 ± 15	15 ± 13
DBP (mm Hg)	10 ± 5	7 ± 5†	12 ± 8	8 ± 6†
HR (beats/min)	11 ± 7	9 ± 6‡	14 ± 16	12 ± 14
RPP (SBP × HR × 10^{-2})	2,625 ± 1,420	1,921 ± 1,178*	3,508 ± 3,770	2,966 ± 3,220
Epinephrine (pg/ml)	36.9 ± 30.8	25.1 ± 17.6§	53.9 ± 58.2	41.9 ± 29.8
Norepinephrine (pg/ml)	42.4 ± 81.7	37.3 ± 106.2	90.4 ± 143.8	75.5 ± 106.8

Mean ± standard deviation change scores (task–rest) to the mental arithmetic.
DBP = diastolic blood pressure; HR = heart rate; RPP = double product; SBP = systolic blood pressure. * $p < 0.001$; † $p < 0.01$; ‡ $p < 0.05$; § $p < 0.10$; all comparisons are between time 1 and time 2 within each group.

attended all scheduled sessions. Strength subjects attended an average of 27.2 sessions (range 15 to 35). Ninety-four percent of the subjects attended all scheduled classes. Participants in the strength group almost tripled their leg strength (18.5 to 50.9 kg, $p < 0.001$) and doubled their arm strength (29.3 to 57.6 kg, $p < 0.001$).

Aerobic fitness: To document changes in cardiorespiratory fitness, 4 variables were selected from the measurements obtained during exercise treadmill testing. These variables included heart rate at rest and at 5 METs, total treadmill time and peak $\dot{V}O_2$. Results of the multivariate analysis of variance yielded a significant time main effect, multivariate $F(4,28) = 25.82$, $p < 0.0001$, and a significant time × group interaction, multivariate $F(4,28) = 11.37$, $p = 0.0001$. Examination of the univariate time × group interactions revealed significant effects for heart rate at rest, $F(1,31) = 18.66$, $p < 0.0001$; total treadmill time, $F(1,31) = 32.95$, $p < 0.0001$; and peak $\dot{V}O_2$ $F(1,31) = 15.61$, $p < 0.0004$.

There were no differences between the aerobic and strength groups at time 1. Table I lists the pattern of change in cardiovascular function. Subjects in the aerobic group experienced significant reductions in heart rate at rest and at 5 METs, and increased their treadmill time by almost 2 minutes. Subjects in the aerobic group increased their peak $\dot{V}O_2$ by 14% ($p < 0.001$), whereas subjects in the strength training group increased their peak by only 3% (difference not significant). Therefore, the exercise interventions were successful in inducing differential improvements in aerobic fitness.

Psychophysiologic responses: A 2 (group) × 3 (phase) analysis of variance at time 1 did not reveal any group main effects or phase × group interactions. Thus, the 2 groups were not different before beginning the respective exercise programs. To assess changes in psychophysiologic responses to the mental arithmetic test, cardiovascular data were first analyzed by a 2 (group) × 2 (time) × 3 (phase) multivariate analysis of variance. This procedure resulted in significant multivariate main effects for phase, $F(6,28) = 22.20$, $p < 0.0001$ and time, $F(3,31) = 12.62$, $p < 0.0001$, and a significant group × time interaction, $F(3,30) = 4.29$, $p < 0.02$, as well as a significant phase × time interaction, $F(6,28) = 3.86$, $p < 0.01$. The time main effect and the phase × time interaction most likely reflected habituation, with lower cardiovascular levels, during the mental arithmetic task at time 2 relative to time 1 for both the aerobic and strength groups. The phase main effect reflected the effectiveness of the task in eliciting robust cardiovascular responses. Significant univariate time × group interactions were found for heart rate, $F(1,32) = 9.88$, $p < 0.01$; double product, $F(1,32) = 10.44$, $p < 0.01$; and diastolic blood pressure, $F(1,32) = 3.99$, $p < 0.054$. Figure 1 shows that heart rate was significantly lower for the aerobic group compared to the strength group at time 2. The aerobic group experienced a 15% reduction in heart rate, $F(1,18) = 47.20$, $p < 0.001$, whereas the strength group experienced a 5% reduction (difference not significant). Similarly, Figure 2 shows that the double product was lower for the aerobic group compared to the strength group. The aerobic group experienced an overall 16% reduction in the double product, $F(1,18) = 44.30$, $p < 0.001$, whereas the strength group experienced a 5% reduction, $F(1,14) = 4.60$, $p < 0.05$. Figure 3 shows that there was also a tendency for diastolic blood pressure to be lower for the aerobic group at time 2, but not for the strength group. The aerobic group experienced a significant 5% reduction in diastolic blood pressure, $F(1,18) = 29.59$, $p < 0.001$, whereas the strength group only experienced a 1% reduction (difference not significant). The pattern of results of the cardiovascular data was unchanged when baseline values for each session were used as covariates in the analyses of variance.

Analysis of the neuroendocrine data revealed a significant main effect for phase, $F(2,24) = 19.08$, $p < 0.0001$, and a marginally significant group × time × phase interaction for epinephrine, $F(2,24) = 2.71$, $p = 0.086$. The phase × time interaction for the strength group was not significant. However, the phase × time interaction was marginally significant for the aerobic group, $F(1,13) = 2.99$, $p < 0.09$. Post-hoc tests of simple effects revealed that epinephrine values tended to be lower at time 2 during the recovery phase, $F(1,14) = 4.04$, $p < 0.07$. Although results did not reach statistical significance, levels during the task phase also tended to be lower (Figure 4). Results were identical when baseline epinephrine values were used as covariates in the analysis of variance.

Analysis of the norepinephrine data revealed a phase main effect, $F(2,24) = 9.49$, $p < 0.001$, with norepi-

nephrine levels greater during the task phase than during baseline or at recovery. Neither the time main effect nor the time × group interaction reached statistical significance, however.

Analysis of change scores: In addition to the analyses described above, a series of analyses of covariance were performed on the change scores (i.e., task − rest) to assess reactivity to the mental arithmetic task. For each of the dependent variables, the preceding baseline served as a covariate in the analysis to adjust for shifts in baseline values. This is a conservative procedure, because the intervention was designed to affect baseline

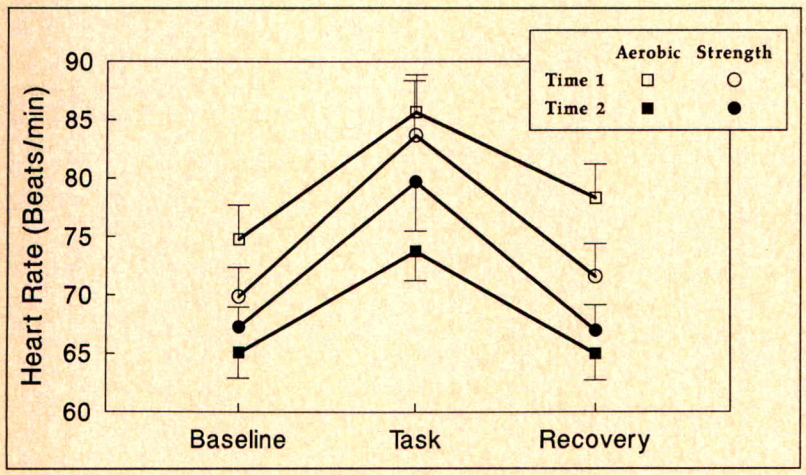


FIGURE 1. Mean heart rate (± standard error) at baseline, task and recovery for the aerobic exercise group and the strength training group at time 1 and time 2.

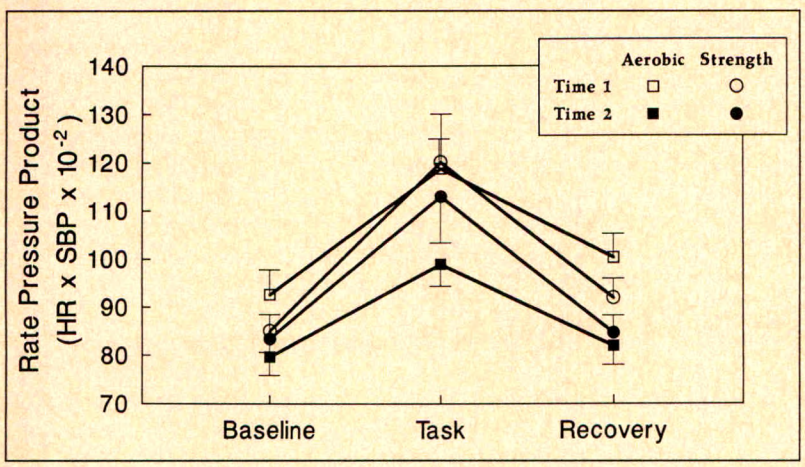


FIGURE 2. Mean rate pressure product (± standard error) at baseline, task and recovery for the aerobic exercise group and the strength training group at time 1 and time 2.

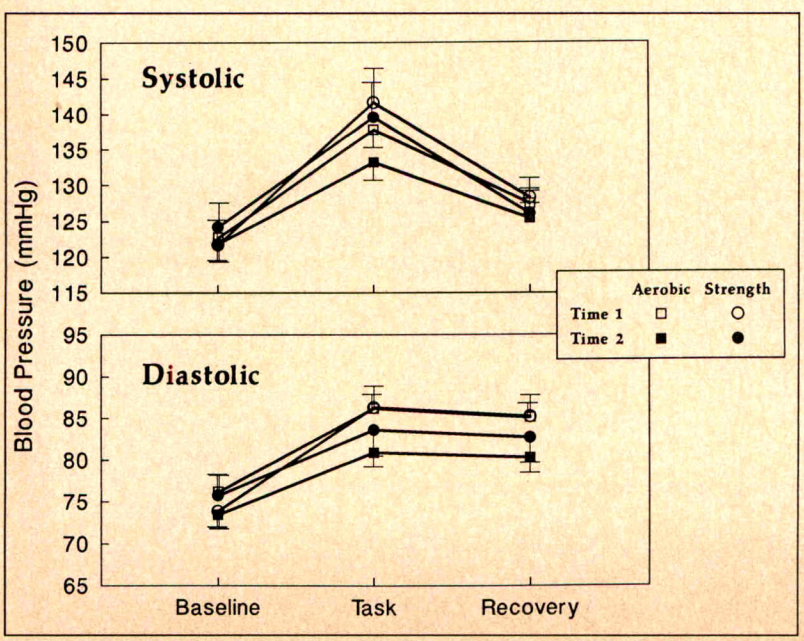


FIGURE 3. Mean systolic blood pressure and diastolic blood pressure (± standard error) at baseline, task and recovery for the aerobic exercise group and the strength training group at time 1 and time 2.

values, as well as levels during the mental stress. A 2 (group) × 2 (time) analysis of covariance of the change scores revealed a significant time main effect for diastolic blood pressure, $F(1,31) = 10.85$, $p < 0.01$, and epinephrine, $F(1,26) = 4.34$, $p < 0.05$, and a marginally significant time main effect for heart rate, $F(1,31) = 3.66$, $p < 0.07$, suggesting that both groups experienced reductions in diastolic blood pressure reactivity, epinephrine reactivity and heart rate reactivity. Although there were no significant group main effects, and the group × time interaction was not significant, within-group comparisons revealed that only the aerobic group experienced a statistically significant attenuation of blood pressure, heart rate and double product, and a marginally significant reduction of epinephrine reactivity to the mental stress (Table II). Although the responses of the strength group were in the same direction, only a reduction in diastolic blood pressure achieved statistical significance. These analyses suggest that aerobic exercise training tended to be associated with greater attenuation of cardiovascular reactivity than strength training.

DISCUSSION

Although numerous cross-sectional studies have associated increased levels of physical fitness with lower levels of autonomic responses to mental stressors,[10] to our knowledge there have been only 4 published longitudinal studies, and they have yielded conflicting results. In a randomized controlled study comparing aerobic exercise, weight training and stress management, Roskies et al[14] reported that no intervention reduced cardiovascular stress responses. Two other studies found that an aerobic exercise group had lower heart rates during a mental arithmetic memory task[12] or after a series of mental stressors,[13] but these findings only characterized a subgroup of subjects who were relatively unfit initially. Moreover, Holmes and McGilley[12] did not randomly assign subjects to exercise conditions and Sinyor et al[13] failed to find significant changes in cardiovascular responses in their primary analyses. In contrast, we reported that aerobic exercise attenuated cardiovascular responses to mental arithmetic.[15] The results of the present investigation provide support for our previous findings. The significant group × time interaction indicates that the exercise programs produced a differential effect on the cardiovascular responses to mental arithmetic. Levels of heart rate, double product (an indirect measure of myocardial $\dot{V}O_2$) and diastolic blood pressure were significantly lower during mental arithmetic for the aerobic group than for the strength group after the 3-month exercise training programs. The reductions observed during and after the mental stress for the aerobic group were significant over and above the reductions in resting baseline levels after aerobic training.

Previous studies have failed to find reductions in stress reactivity.[12–14] Our data provide modest support for reduction of stress reactivity insofar as the group × time interaction was not statistically significant. Although within-group comparisons revealed reduced reactivity for the aerobic group and not for the strength group, the greater variability (larger standard deviations) of responses in the strength group made it difficult to achieve statistical significance. Correlations of change in peak $\dot{V}O_2$ (from time 1 to time 2) with change in reactivity ranged from 0.03 (systolic blood pressure) to 0.36 (epinephrine); no correlation reached statistical significance. Thus, there was only a tendency for greater reactivity reduction in the aerobic group, and increased aerobic fitness was not associated with reduced stress reactivity. We conclude that aerobic exercise is more likely to reduce overall *levels* of cardiovascular response, rather than reduce the magnitude of absolute *change* of responses from rest to mental stress.

To our knowledge our study is also the first randomized, longitudinal study to document changes in both

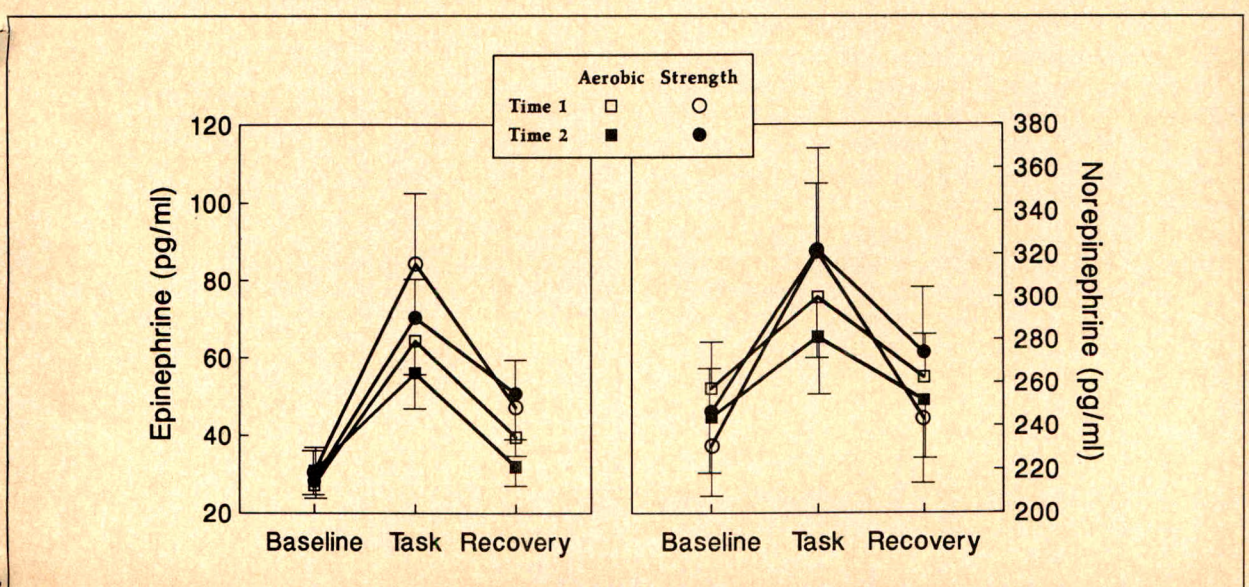


FIGURE 4. Mean epinephrine (*left*) and norepinephrine (*right*) responses (± standard error) at baseline, task and recovery for the aerobic exercise group and the strength training group at time 1 and time 2. Blood samples could not be obtained for 10 subjects either at time 1 or time 2. Therefore, the number of subjects for whom catecholamine data were available was 27.

cardiovascular and catecholamine responses to mental stress. In a cross-sectional study, Sinyor et al[19] reported that epinephrine and norepinephrine levels were higher in fit subjects, and showed a faster recovery compared to unfit subjects. However, Dorheim et al[20] failed to observe differences in neuroendocrine responses to a series of behavioral stressors among a group of marathon runners and an age-matched group of untrained individuals. Similarly, Hull et al[21] failed to find differences in catecholamine responses to a series of stressors in fit and unfit subjects. In a recent study, Sinyor et al[22] failed to show a reduction in epinephrine levels after 10 weeks of aerobic exercise. Although their data appear to have resembled ours, the observed reductions did not reach statistical significance. Because they only studied 6 subjects, however, it is unlikely that they had enough statistical power to detect any changes. Our present data indicate that epinephrine but not norepinephrine levels tended to be reduced after a program of aerobic exercise training. One reason for the failure to find a reduction in norepinephrine levels is that the norepinephrine response to mental arithmetic was comparatively small relative to the epinephrine response. Selection of a stressor that would elicit a more significant norepinephrine response may be necessary to demonstrate the effects of exercise training on norepinephrine responsiveness.

Taken together, these findings provide evidence for the efficacy of aerobic exercise in reducing levels of cardiovascular and sympathoadrenal responses to mental stress. However, it is not clear why we have been able to demonstrate the effectiveness of the aerobic exercise intervention while others have not. We suspect that differences in subject characteristics, experimental design, selection of mental stressors and procedures for exercise training and testing may be important. Future research should be directed at identifying those aspects that may be critical for understanding the differences among studies.

Although our data suggest that significant improvements in cardiorespiratory fitness may serve to reduce sympathetically mediated responses to moderate mental stress, the clinical significance of these findings should be more carefully evaluated. Because it has been suggested that the relation between behavioral factors and coronary artery disease may be mediated by the frequent and sustained activation of the sympathetic-adrenomedullary and pituitary-adrenocortical systems,[9] attenuation of these responses may be beneficial. Indeed, animal studies have noted that surgically lowering heart rate is associated with slower progression of coronary disease,[23] and administration of β-adrenergic blockade also slows disease progression, potentially by attenuating cardiovascular activation.[24] Further studies are needed to document the clinical benefits of regular aerobic training in humans, and to elucidate the mechanisms by which exercise alters psychophysiologic stress responses.

Acknowledgment: We wish to thank Susan Schniebolk, Robin Pomeroy, Cherie Rich and Sally Schnitz for technical support, and Janet Ivey for secretarial assistance.

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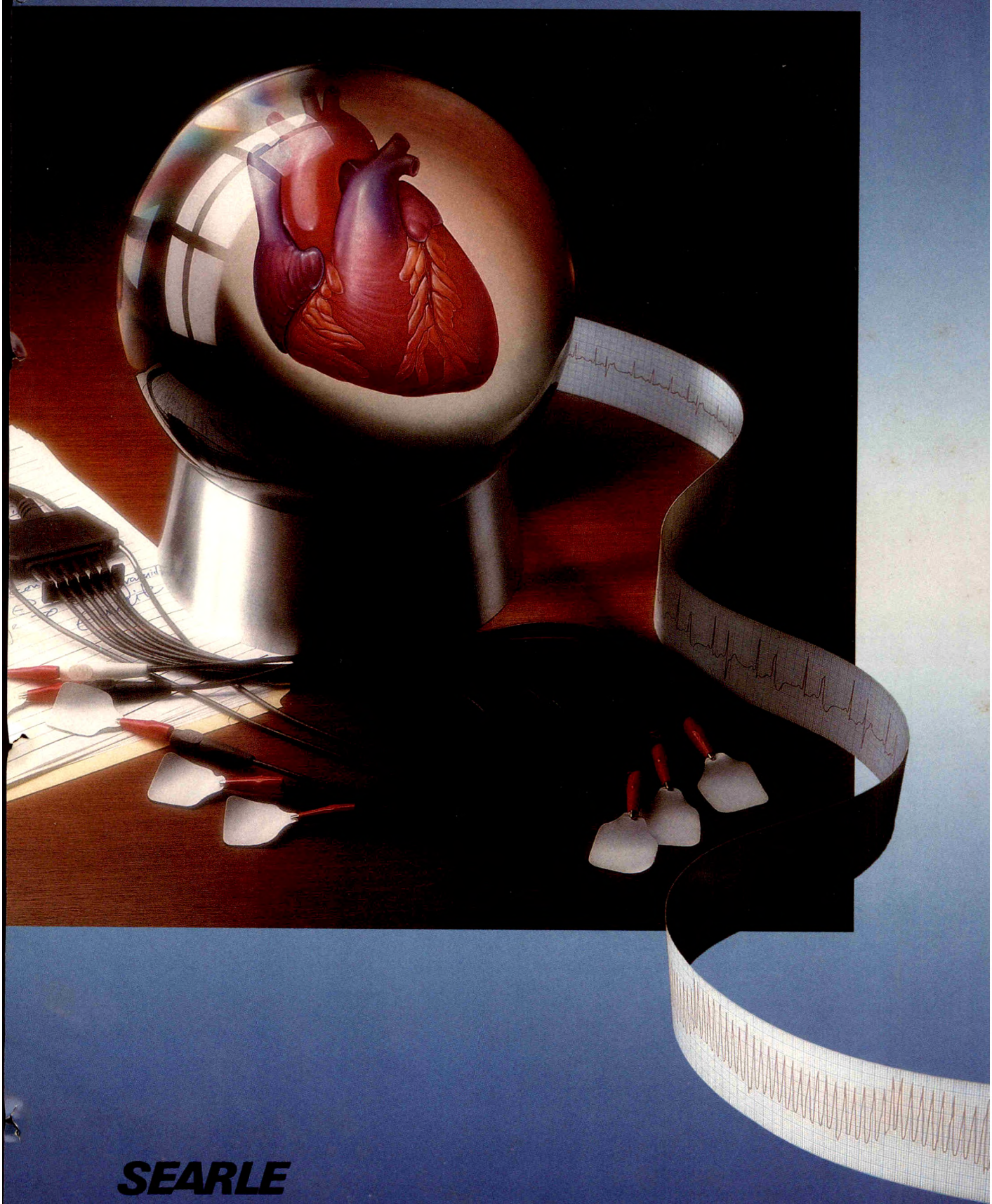
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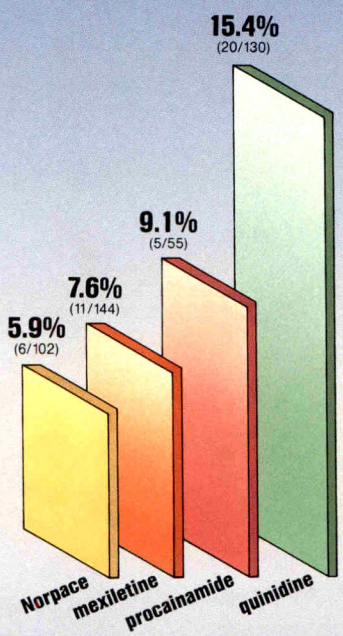
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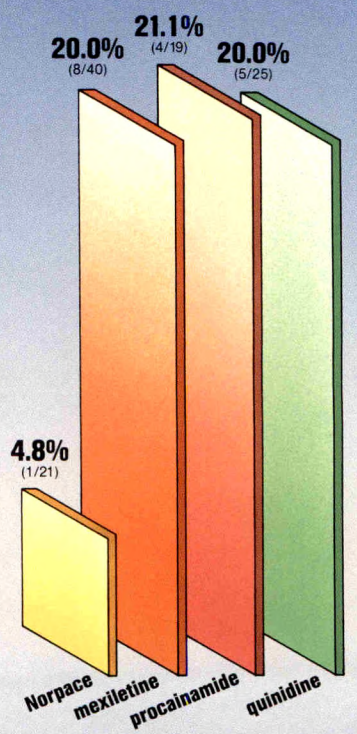
Predictability, short-term

Clinical studies have found Norpace® (disopyramide phosphate) to have a low incidence of proarrhythmia.[1,2]

Frequency of aggravation of arrhythmia among selected agents tested[1,2]



Adapted from Velebit et al.[1]
Results based on noninvasive testing.



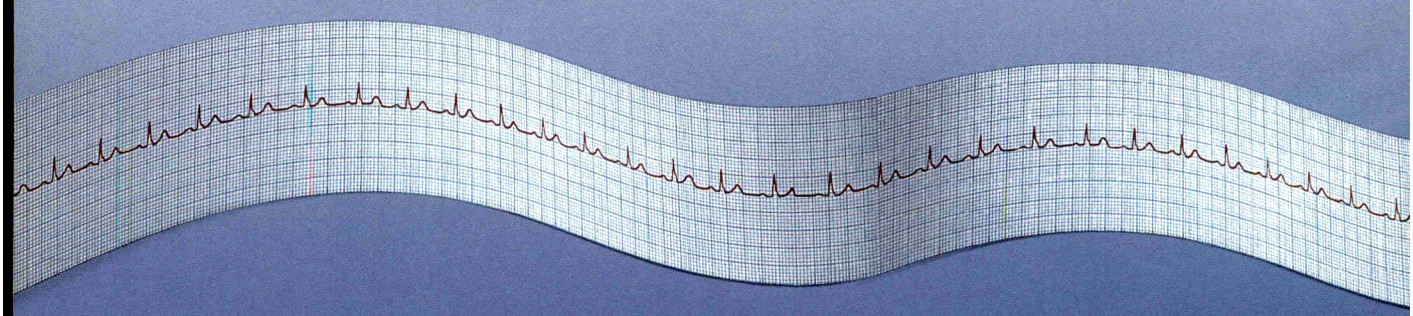
Adapted from Poser et al.[2]
Results based on invasive testing.

Predictable side effects

Norpace CR is generally well tolerated. The side effects are usually dose-related and generally not a cause for drug withdrawal in well-chosen patients.[3]

The most commonly seen side effects of disopyramide phosphate are anticholinergic, and the most severe are due to its negative inotropic properties.

Disopyramide is contraindicated in patients with a history of cardiogenic shock, preexisting second- or third-degree AV block (if no pacemaker is present), congenital Q-T prolongation, or known hypersensitivity to the drug.

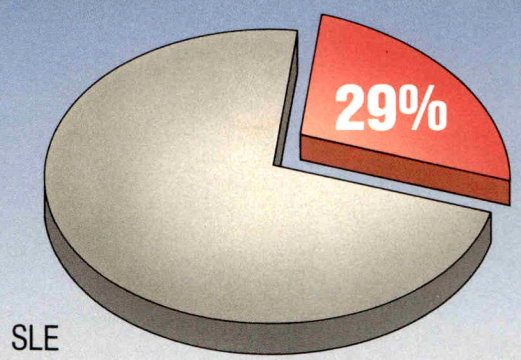


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Predictability, long-term

Norpace (disopyramide phosphate) is rarely associated with late-appearing toxicities such as lupus and agranulocytosis.[4]

Incidence of lupus (SLE*) with procainamide[5]



Adapted from Henningsen et al.[5]

During a five-year follow-up study, 29% (12/42) of patients developed a classic drug-induced SLE syndrome.[5] Additional studies confirm this frequent adverse reaction.[4,6]

*Systemic lupus erythematosus.

Results of a long-term follow-up (up to 64 months) of patients on Norpace (disopyramide phosphate):

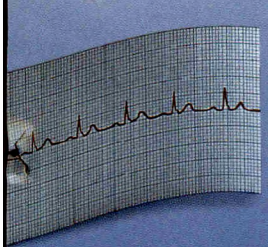
- In 60% (24/40) of patients, Norpace provided effective and tolerated monotherapy for up to 64 months.[7]
- Anticholinergic side effects, although common, were usually tolerated.[7]

Predictable therapy

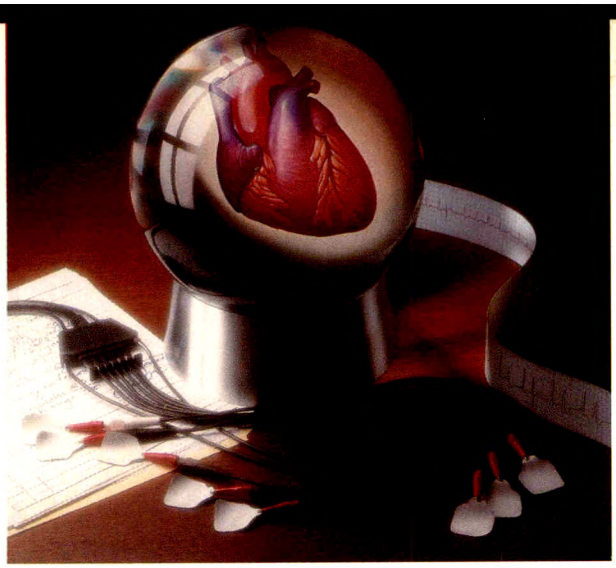
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Predictable monotherapy

- Effective first-line antiarrhythmic control comparable to that of quinidine.[8]

Predictability, short-term

- Side effects are usually manageable.
- Not generally associated with hypersensitivity reactions.
- Low incidence of proarrhythmia.[2,4]

Predictability, long-term

- Few late-appearing adverse reactions such as lupus or agranulocytosis.
- Low drop-out rate as compared with quinidine.[8]
- Established safety profile through 12 years of use.

References: 1. Velebit V, Podrid P, Lown B, et al: Aggravation and provocation of ventricular arrhythmias by antiarrhythmic drugs. *Circulation* 1982;65:886-894. **2.** Poser RF, Podrid PJ, Lombardi F, et al: Aggravation of arrhythmia induced with antiarrhythmic drugs during electrophysiologic testing. *Am Heart J* 1985;110 (July):9-16. **3.** Ekelund L-G: Clinical experience with controlled-release disopyramide. *Practical Cardiology* (special issue), June 1988, pp 38-42. **4.** DiBianco R, Larca LJ, Singh SN, et al: A comprehensive clinical review of the standard, oral antiarrhythmic agents. *Cardiovasc Rev Rep* 1985;6:625-646. **5.** Henningsen NC, Cederberg A, Hanson A, et al: Effects of long-term treatment with procaine amide: A prospective study with special regard to ANF and SLE in fast and slow acetylators. *Acta Med Scand* 1975; suppl 198, pp 475-482. **6.** Kosowsky BD, Taylor J, Lown B, et al: Long-term use of procaine amide following acute myocardial infarction. *Circulation* 1973;47:1204-1210. **7.** Bauman JL, Gallastegui J, Strasberg B, et al: Long-term therapy with disopyramide phosphate: Side effects and effectiveness. *Am Heart J* 1986;111:654-660. **8.** Arif M, Laidlaw JC, Oshrain C, et al: A randomized, double-blind, parallel group comparison of disopyramide phosphate and quinidine in patients with cardiac arrhythmias. *Angiology* 1983;34:393-400.

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Norpace® Capsules
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Norpace® CR Capsules
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Brief Summary

Before prescribing, please consult current complete prescribing information, a summary of which follows: **Indications:** For suppression and prevention of recurrence of the following cardiac arrhythmias: unifocal premature (ectopic) ventricular contractions; premature (ectopic) ventricular contractions of multifocal origin; paired premature ventricular contractions (couplets); and episodes of ventricular tachycardia (persistent ventricular tachycardia is ordinarily treated with DC-cardioversion). Norpace is equally effective in both digitalized and nondigitalized patients. It is also equally effective in treating primary cardiac arrhythmias and those which occur in association with organic heart disease including coronary artery disease. Norpace CR should not be used initially if rapid establishment of disopyramide plasma levels is desired. Oral disopyramide phosphate has not been adequately studied in patients with acute myocardial infarction or with persistent ventricular tachycardia or atrial arrhythmias and is not indicated for arrhythmias due to digitalis intoxication. The value of antiarrhythmic drugs in preventing sudden death in patients with serious ventricular ectopic activity has not been established. **Contraindications:** Cardiogenic shock, preexisting second- or third-degree AV block (if no pacemaker is present), congenital Q-T prolongation, or known hypersensitivity to the drug. **Warnings: Norpace or Norpace CR may cause or worsen congestive heart failure (CHF) or produce severe hypotension as a consequence of its negative inotropic properties. Hypotension has been observed primarily with primary cardiomyopathy or inadequately compensated CHF. Norpace or Norpace CR should not be used in patients with uncompensated or marginally compensated CHF or hypotension unless the condition is secondary to cardiac arrhythmia. Patients with a history of heart failure may be treated with Norpace or Norpace CR, but careful attention must be given to maintaining cardiac function, including optimal digitalization. If hypotension occurs or CHF worsens, Norpace or Norpace CR should be discontinued and, if necessary, restarted at a lower dosage only after adequate cardiac compensation has been established. Norpace or Norpace CR should be discontinued if significant widening (greater than 25%) of the QRS complex occurs. Prolongation of the Q-T interval (corrected) and worsening of the arrhythmia may occur. Patients who have evidenced prolongation of the Q-T interval in response to quinidine may be at particular risk. As with other Type 1A antiarrhythmics, disopyramide has been associated with torsade de pointes. If Q-T prolongation greater than 25% is observed and if ectopy continues, the patients should be monitored closely, and discontinuation of Norpace or Norpace CR considered. In rare instances significant hypoglycemia has been reported during Norpace therapy. The concomitant use of Norpace or Norpace CR with other Type 1 antiarrhythmic agents and/or propranolol should be reserved for patients with life-threatening arrhythmias who are demonstrably unresponsive to single agent antiarrhythmic therapy. Such use may produce serious negative inotropic effects, or may excessively prolong conduction. Patients receiving more than one antiarrhythmic drug must be carefully monitored. If first-degree heart block develops, the dosage of Norpace or Norpace CR should be reduced. If the block persists, continuation of Norpace or Norpace CR must depend upon an assessment of benefit versus risk. Development of second- or third-degree AV block or uni-, bi-, or trifascicular block requires discontinuation of drug unless the ventricular rate is adequately controlled by a pacemaker. Because of its anticholinergic activity, disopyramide phosphate should not be used in patients with glaucoma, myasthenia gravis, or urinary retention unless adequate overriding measures are taken. In patients with a family history of glaucoma, intraocular pressure should be measured before initiating Norpace or Norpace CR therapy. Precautions:** Patients with atrial flutter or fibrillation should be digitalized prior to Norpace or Norpace CR administration to ensure that drug-induced enhancement of AV conduction does not allow a ventricular rate beyond physiologically acceptable limits. The effect of Norpace or Norpace CR is presently uncertain in patients with sick sinus syndrome, Wolff-Parkinson-White syndrome, or bundle branch block. Patients with myocarditis or other cardiomyopathy may develop significant hypotension in response to the usual dosage of disopyramide phosphate. Therefore, a loading dose of Norpace should not be given to such patients, and initial dosage and subsequent dosage adjustments should be made under close supervision. Norpace dosage should be reduced in patients with impaired renal or hepatic function and the electrocardiogram carefully monitored for signs of overdosage. Norpace CR is not recommended for patients with severe renal insufficiency. Antiarrhythmic drugs may be ineffective in patients with hypokalemia, and their toxic effects may be enhanced in patients with hyperkalemia. Therefore, potassium abnormalities should be corrected before starting Norpace or Norpace CR therapy. Concomitant administration of disopyramide phosphate with phenytoin or other hepatic enzyme inducers may cause lower disopyramide plasma levels. Concomitant administration with other antiarrhythmics may cause excessive widening of the QRS complex and/or prolongation of the Q-T interval. Concomitant administration with quinidine resulted in slight increases in disopyramide levels and slight decreases in quinidine levels. Pregnancy Category C. Norpace was associated with decreased numbers of implantation sites and decreased growth and survival of pups when administered to pregnant rats at 250 mg/kg/day, a level at which weight gain and food consumption of dams were also reduced. Increased resorption rates were reported in rabbits at 60 mg/kg/day. Safe use in pregnancy has not been established. Disopyramide has been found in human fetal blood. **Norpace has been reported to stimulate contractions of the pregnant uterus.** Use of Norpace or Norpace CR in pregnant women requires that the potential benefit be weighed against possible hazards to the fetus. Effects of Norpace or Norpace CR on the fetus during delivery or on the course of labor and delivery are unknown. Following oral administration, disopyramide has been found in human milk at a concentration not exceeding that in plasma. Because of the potential for serious adverse reactions in nursing infants from Norpace or Norpace CR, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. **Adverse Reactions:** Dry mouth, urinary hesitancy, constipation, blurred vision, dry nose/eyes/throat, urinary retention especially in males with benign prostatic hypertrophy, urinary frequency and urgency, impotence, nausea, pain/bloating/gas, anorexia, diarrhea, vomiting, nervousness, dizziness, general fatigue/muscle weakness, headache, malaise, aches/pains, hypotension, congestive heart failure, cardiac conduction disturbances, edema/weight gain, shortness of breath, syncope, chest pain, generalized rash/dermatoses, itching, hypokalemia, elevated cholesterol/triglycerides, depression, insomnia, dysuria, numbness/tingling, elevated liver enzymes, AV block, elevated BUN, elevated creatinine, decreased hemoglobin/hematocrit, and hypoglycemia. Acute psychosis, cholestatic jaundice, and agranulocytosis, all three reversible, have been reported, as have fever, respiratory difficulty, thrombocytopenia, and gynecomastia. Some cases of lupus erythematosus (LE) symptoms have occurred, mostly in patients switched from procainamide to disopyramide following the development of LE symptoms. **Dosage and Administration:** Dosage must be individualized on the basis of response and tolerance. The usual adult dosage is 400 to 800 mg/day given in divided doses: q6h for Norpace and q12h for Norpace CR. **See current complete prescribing information for dosage recommendations.**

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Effects of Nifedipine on the Venodilatory Response to Nitroglycerin

Joseph A. Gascho, MD, and William P. Apollo, BS

The venodilatory effect of nifedipine 10 mg orally and the venodilatory effect of nitroglycerin 0.8 mg spray after pretreatment with nifedipine were assessed in 15 healthy men aged 22 to 41 years. Compared to placebo, nifedipine caused arteriolar dilation but did not venodilate (control VV[30] 3.67 ± 0.24 [mean ± standard error of the mean], after nifedipine VV[30] 3.41 ± 0.22 cc/100 cc arm). The venodilatory effect of nitroglycerin was not altered by pretreatment with nifedipine. VV[30] increased by 0.72 ± 0.14 cc/100 cc arm after nitroglycerin in subjects pretreated with placebo compared to 0.70 ± 0.09 cc/100 cc arm in subjects pretreated with nifedipine. These results suggest that, at a dose of 10 mg, nifedipine does not venodilate and the venodilatory effect of nitroglycerin is not altered by pretreatment with nifedipine.

(Am J Cardiol 1990;65:99–102)

From the Milton S. Hershey Medical Center, Pennsylvania State University, Division of Cardiology, Hershey, Pennsylvania. Manuscript received June 28, 1989; revised manuscript received and accepted August 25, 1989.

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Patients with symptomatic coronary artery disease frequently take both calcium antagonists and nitrates. Calcium antagonists dilate arterioles.[1] Some studies suggest that these agents dilate veins or attenuate venoconstriction induced by agents such as potassium chloride[1–4]; others suggest they do not venodilate.[5–7] Glyceryl trinitrates, such as nitroglycerin, dilate both arterioles and veins. At low doses, the predominant effect is venodilation.[8] The purposes of the present study were to determine, using a standard limb plethysmographic technique, if nifedipine venodilates and if the venodilatory effect of nitroglycerin is altered in subjects pretreated with nifedipine.

METHODS

Patient population: Fifteen healthy male volunteers, age 22 to 41 years, were studied. None was taking any medication. Subjects gave informed consent and this institute's Committee on Human Research approved the study protocol.

Determination of venous distensibility: The equilibration technique was used to measure venous distensibility.[9,10] This technique consists of rapidly inflating an upper arm cuff to a pressure 30 mm Hg above cuff zero, allowing venous pressure to equilibrate with cuff pressure. The change in venous volume of the forearm, after equilibration at 30 mm Hg above cuff zero (VV[30]), expressed in cc/100 cc arm, is considered to be an index of venous distensibility. After equilibration, an agent such as nitroglycerin can be administered. A further increase in venous volume with the upper arm cuff still inflated to 30 mm Hg above cuff zero implies venodilation. A single-strand mercury-in-silastic strain gauge[11] is used to measure changes in forearm volume. With this technique, the hand is isolated from the circulation by the application of a wrist cuff to suprasystolic pressure,[12] and the forearm is elevated above heart level to ensure that the veins in the forearm are collapsed.[10]

Because of technical difficulties, venous studies in 1 subject were not interpretable. The venous distensibility data are based on the other 14 subjects.

Determination of forearm vascular resistance: The venous occlusion technique was used to measure forearm blood flow.[11,13–15] Mean arterial pressure was measured by oscillometry, using an automated blood pressure device (Dinamap). Forearm vascular resistance was calculated by dividing mean arterial pressure by forearm flow. The final forearm vascular resistance value at each point in the protocol was determined by averaging values calculated from 6 to 8 measurements.

General protocol instrumentation: Studies were performed in a warm (75°F) quiet room. Subjects were

studied in the supine position with loose clothing on the upper torso. They had not eaten for at least 5 hours and had emptied their bladders before the study. Blood pressure cuffs were placed around the upper right arm, the upper left arm and the left wrist. Strain gauges were secured with tape around both the left and the right forearm. The left arm was positioned so that the portion of the arm encircled by the plethysmograph was above heart level. After instrumentation, subjects were allowed to become acclimated to the surroundings for 15 to 20 minutes. Measurements of venous distensibility were made on the left arm; measurements of forearm blood flow for calculation of forearm vascular resistance were made on the right arm.

Experimental design: Venous distensibility, forearm vascular resistance, arterial pressure and heart rate were measured 3 times: (1) during baseline conditions, 15 to 20 minutes after instrumentation; (2) 30 minutes after either placebo or nifedipine, 10 mg orally; and (3) 6 minutes after nitroglycerin spray (0.8 mg to the top of the tongue) (about 36 minutes after placebo or nifedipine). The study was repeated on another day (usually 1 day later) within 1 hour of the same time of day. Subjects were blinded to treatment (placebo or nifedipine). Nine subjects were given placebo on day 1 and nifedipine on day 2, while 6 were given nifedipine on day 1 and placebo on day 2.

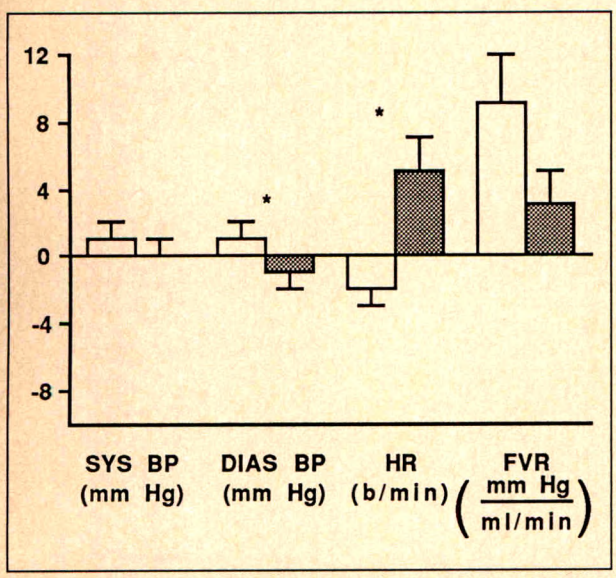


FIGURE 1. Nifedipine caused a greater decrease in diastolic blood pressure (DIAS BP), and a greater increase in heart rate (HR) compared to placebo. *Open bars* represent changes measured after placebo, *stippled bars* after nifedipine. * p ≤0.05. Data are mean ± standard error of the mean. FVR = forearm vascular resistance; SYS BP = systolic blood pressure.

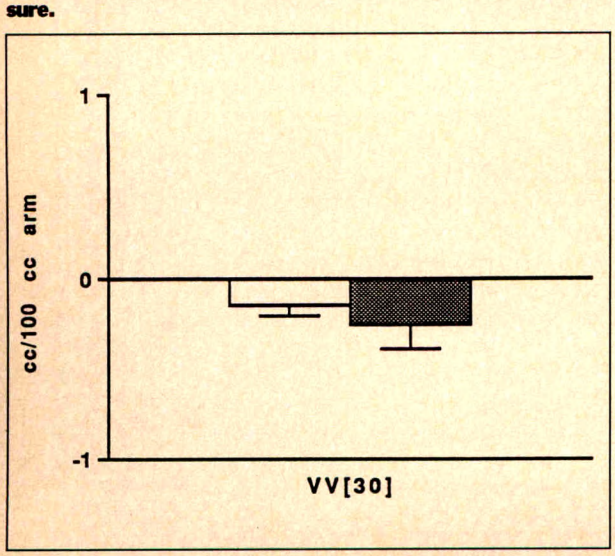


FIGURE 2. There was no difference in the venodilatory response to placebo compared to nifedipine. *Open bar* represents placebo effect; *stippled bar* represents nifedipine effect. Data are mean ± standard error of the mean.

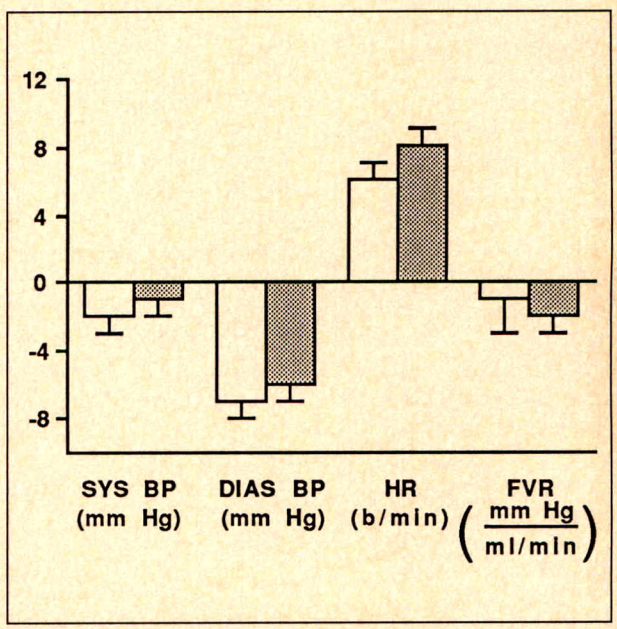


FIGURE 3. The decrease in blood pressure and the increase in heart rate induced by nitroglycerin after pretreatment with nifedipine were similar to the changes induced by nitroglycerin after placebo. *Open bars* represent experiments in which placebo was administered; *stippled bars* = nifedipine. Abbreviations as in Figure 1.

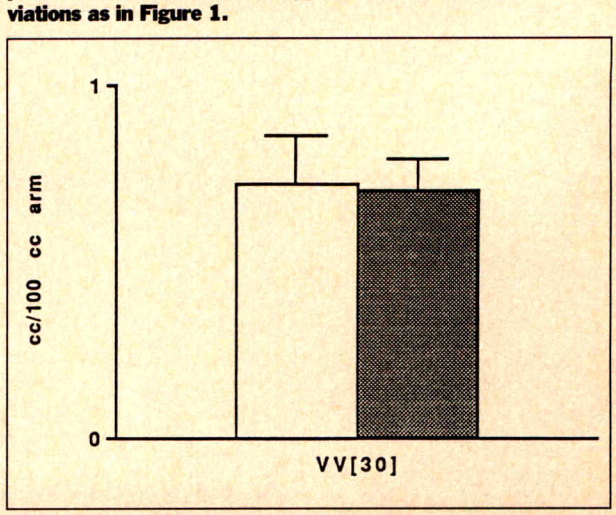


FIGURE 4. The venodilatory response to nitroglycerin after pretreatment with nifedipine was similar to the venodilatory response to nitroglycerin after pretreatment with placebo. Venodilatory effect after pretreatment with placebo is shown by *open bar*, after pretreatment with nifedipine by *stippled bar*. Data are mean ± standard error of the mean.

Statistical analysis: The null hypotheses tested were (1) that changes in hemodynamics and VV[30] induced by placebo were the same as those induced by nifedipine, and (2) that the changes in hemodynamics and VV[30] induced by nitroglycerin after placebo pretreatment were the same as those induced by nitroglycerin after nifedipine pretreatment. Paired *t* tests were used to test each of these null hypotheses. A p value ≤ 0.05 was considered significant.

RESULTS

Effects of placebo and nifedipine on hemodynamics and venous distensibility: The changes in blood pressure, heart rate and forearm vascular resistance induced by placebo and nifedipine are shown in Figure 1. There was no difference between the effects of placebo and nifedipine on systolic blood pressure and forearm vascular resistance, but compared to placebo, nifedipine caused a decrease in diastolic pressure and an increase in heart rate. There was no difference between the effects of placebo and nifedipine on VV[30] (Figure 2).

Effects of nitroglycerin on hemodynamics and venous distensibility after pretreatment with placebo and nifedipine: The decrease in blood pressure, the increase in heart rate and the change in forearm vascular resistance induced by nitroglycerin after pretreatment with placebo were similar to the effects induced by nitroglycerin after pretreatment with nifedipine (Figure 3). There was no difference between the increase in VV[30] induced by nitroglycerin after placebo pretreatment compared to the increase induced by nitroglycerin after nifedipine pretreatment (Figure 4).

The changes in VV[30] induced by nitroglycerin in this study were similar to the changes in VV[30] induced by nitroglycerin in previous studies performed in our laboratory.[16–18]

DISCUSSION

Our results demonstrate that nifedipine in a dose of 10 mg does not dilate forearm veins, and that nifedipine does not alter the venodilatory response to nitroglycerin.

Some experiments in both animals and humans have suggested that nifedipine may venodilate. Church and Zsoter[4] noted that nifedipine markedly attenuated spontaneous contractile activity of rat portal veins, and that the contractions induced by norepinephrine and potassium chloride were inhibited by nifedipine. However, portal veins undergo spontaneous depolarization, and may be more dependent on potential-dependent calcium channels than other veins that do not contract spontaneously. Mikkelsen et al showed that nifedipine relaxed strips of human peripheral veins[2] and mesenteric veins[3] contracted by norepinephrine or potassium chloride. In experiments by Robinson et al,[1] nifedipine attenuated the venoconstriction induced by the in vivo infusion of potassium chloride, but not the venoconstriction induced by norepinephrine.

In contrast Houston et al,[5] using venous plethysmography, found no increase in venous compliance after nifedipine 10 mg was administered sublingually to patients with hypertension or to control subjects with normal blood pressure. Neither Manyari et al[6] nor Nakamura et al[7] noted venodilation of forearm veins after sublingual nifedipine 20 mg.

Our findings support these latter 3 studies. In our experiments, nifedipine did not dilate veins. It is difficult to compare our experiment to that by Robinson et al[1] because they used a different technique (a lightweight level positioned on a hand vein, used to quantitate displacement) and a different protocol (venodilation was assessed in precontracted veins). In the in vitro experiments, systemic humoral and nervous system influences are not present. In addition, it is difficult to extrapolate in vitro drug concentrations to in vivo blood levels.

The change in forearm vascular resistance after nifedipine was not significantly different from the change after placebo. This suggests that arteriolar resistance in the forearm was not decreased by nifedipine. Nifedipine appears to have produced significant arteriolar dilations in other vascular beds. Compared to the placebo arm of the protocol, nifedipine caused diastolic blood pressure to decrease and heart rate to increase.

Although various investigators have shown that nitroglycerin venodilates forearm veins,[6,16–20] there is little, if any, information about the effect of a calcium antagonist on the venodilatory effect of nitroglycerin. Even if nifedipine does not venodilate, the venodilatory effect of nitroglycerin in subjects treated with nifedipine might be altered. For example, the reflex increase in sympathetic tone caused by the arteriolar dilatory effect of nifedipine might attenuate the venodilatory response to nitroglycerin. We did not note any difference between the venodilatory response to nitroglycerin after nifedipine compared to the response after placebo.

It is possible that larger doses of nifedipine would have caused venodilation. However, there was not even a trend for venodilation at the 10-mg dose, which caused arteriolar dilation. Blood levels of nifedipine were not measured in this study. Other studies have demonstrated therapeutic levels at 30 minutes after administration.[21]

The technique we used measured the venodilatory response of forearm veins. The venodilatory response of another important bed, the splanchnic bed, was not assessed. Although 1 group of investigators using radionuclide techniques noted that the forearm and splanchnic bed responded similarly to nitroglycerin,[22] others believe the splanchnic bed may respond differently to a vasoactive agent than forearm veins.[5,23]

Clinical implications: The present study suggests that the venodilatory effect of nitroglycerin is not attenuated by pretreatment with calcium antagonists.

Acknowledgment: We thank Robert Zelis, MD, for reviewing the manuscript, Dwane Gehman and Heidi Leaman for technical assistance, and Sandra Whisler for secretarial assistance.

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Clinical and Regulatory Implications of the Cardiac Arrhythmia Suppression Trial

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Occasionally, a study is published that has a profound impact on an area of contemporary cardiology. Such a study, the Cardiac Arrhythmia Suppression Trial (CAST),[1] was published recently. The CAST promises to exert considerable influence on our concepts regarding ventricular arrhythmias and sudden (arrhythmic) death for some time to come. As a direct result of the CAST, a special meeting of the Cardiovascular and Renal Drugs Advisory Board to the Food and Drug Administration (FDA) was held to discuss the implications of the CAST in a public forum. As members of that committee, we were asked to share our personal opinions on the importance of the CAST findings as they relate to clinical practice and the drug regulatory process. The minutes of the entire committee proceedings are public record.

The Cardiac Arrhythmia Suppression Trial: The magnitude of the mortality result of the CAST was quite surprising. The CAST was comprised of patients with asymptomatic ventricular arrhythmias after acute myocardial infarction, a patient population usually thought to be at moderately increased risk of arrhythmic death. The CAST was designed to test the hypothesis that the suppression of ventricular premature complexes (VPCs) by antiarrhythmic drugs would reduce arrhythmic death risk. However, over a treatment duration averaging 10 months, patients receiving encainide and flecainide had a 3.64-fold increase in arrhythmic death/cardiac arrest compared to their respective placebo group.[1] The inclusion of a parallel placebo group was invaluable in making the observation that an excess of arrhythmic deaths with encainide and flecainide occurred throughout the duration of the study. In this temporal respect, the increase in arrhythmic deaths defied traditional concepts of proarrhythmia, usually thought of as occurring within days or weeks of initiating therapy.[2,3] This proarrhythmia was even more disturbing since the CAST patients randomized to receive encainide and flecainide had already been shown to tolerate the drugs and even demonstrated VPC suppression during an open-label, dose-titration phase. Thus, a high proarrhythmic death rate in the CAST occurred despite the appropriate testing of these drugs with standard clinical assessments before randomization to eliminate patients with obvious proarrhythmia, increasing heart failure or other drug toxicity, as well as nonresponders.

The mortality results are of sufficient magnitude to merit a reconsideration of our traditional concepts of proarrhythmia. The CAST subgroup analyses revealed a remarkably consistent increase in mortality associated with the use of encainide and flecainide.[1] These preliminary CAST results do not offer any encouragement that either the clinical endpoint of VPC suppression or treating asymptomatic VPCs is effective in reducing the risk of arrhythmic death. In fact, they should generate a healthy skepticism regarding the use of traditional (1a, 1b, 1c) antiarrhythmic drugs in any patient population with VPCs where documented patient benefit has not been demonstrated.

The "database" approach to defining the incidence of proarrhythmia: Until the CAST revelations, it was conventional to define proarrhythmic effects of antiarrhythmic drugs as arrhythmic events that occurred within days or weeks of the initiation of therapy.[2–4] Sudden deaths occurring after months or years of antiarrhythmic therapy were usually considered as either "inefficacy" or "disease progression." The antiarrhythmic drug databases of both encainide and flecainide were reviewed retrospectively using this definition. These database analyses included large populations but had no control group (flecainide, n = 1330; encainide, n = 1755).[4] Despite this large numerical experience, the proarrhythmic potential of these 2 drugs in patients with asymptomatic ventricular arrhythmia was not detected despite the fact that the combined database experience of >3,000 patients exceeded the size of the CAST encainide/flecainide treatment group by 4-fold. The CAST population would be classified as a potentially lethal group with moderate arrhythmic death risk, yet the CAST encainide/flecainide population had a 4.4% arrhythmic mortality within 10 months, even higher than that reported for patients presenting with lethal ventricular arrhythmias in the drug database reports of encainide and flecainide.[4] It is interesting that the mean observation period in the flecainide database was 292 days, nearly identical to the CAST (300 days), and yet a 0.2% incidence of proarrhythmic death for flecainide was reported in the potentially lethal category.[2] The limitations of database analysis include the absence of experience with postinfarction patients and the lack of a parallel placebo group.

The power of the CAST study design: The CAST detected this large proarrhythmic death rate in a "mod-

The authors are members of the Cardiovascular and Renal Drugs Advisory Board to the Food and Drug Administration. Manuscript received October 31, 1989, and accepted November 2.

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erate" risk group because of the power of a parallel placebo-controlled design. These results affirm the necessity of, the rationale for and the ethical validity of pursuing knowledge through randomized, placebo-controlled clinical trials. The excessive arrhythmic death rate observed in the CAST may also have been previously undetected because patients with recent acute myocardial infarction and ventricular arrhythmia, as well as patients with severe left ventricular dysfunction, are almost always excluded from pharmaceutical trials. It is also possible that the proarrhythmic potential of antiarrhythmic drugs may be patient-population specific. Furthermore, the proarrhythmia detected in the CAST may have resulted, at least in part, from an interaction of ischemia, ventricular arrhythmia and the electrophysiologic properties of specific antiarrhythmic drugs. As suggested by Ruskin[5] in his editorial accompanying the CAST report, preliminary data from animal infarct models exist, which suggest that transient episodes of acute ischemia may convert "antiarrhythmic" drugs to "proarrhythmic" drugs.[6] Another potential contributing factor was that by the inclusion of many patients with left ventricular dysfunction in the CAST, the proarrhythmic effects of encainide and flecainide were enhanced.[7]

Regulatory issues raised by the CAST: how should antiarrhythmics be labeled? The discussion was limited to electrophysiologic class 1a, 1b and 1c agents. We feel that extrapolation of the CAST results to other populations and other antiarrhythmic drugs is inevitable. Can the CAST results be extrapolated to the other electrophysiologic class 1c agents; to other electrophysiologic classes (1a, 1b)? To what extent can the CAST results be extended to other patient populations? Although we addressed these questions as regulatory issues, the thrust of the question is equally relevant to clinical practice. Our committee attempted to reach reasonable speculative compromises, given the magnitude of the CAST results.

The committee considered issues related to the labeling of the currently marketed antiarrhythmic drugs. Given the absence of definitive clinical trials of other agents like the CAST, the consensus of the committee favored a conservative approach, emphasizing safety in the absence of data demonstrating patient benefit. For instance, the committee voted to recommend restrictive labeling of other class 1c agents (once approved and marketed) identical to that now required for encainide and flecainide (i.e., limited to life-threatening ventricular arrhythmias).

While the discussion of the committee regarding the 1a and 1b agents reflected considerable concern, it was recommended that a somewhat less restrictive approach be taken on labeling indications of these agents. However, a consensus opinion was that the labeling of all antiarrhythmic agents (1a, 1b, 1c) should be consistently rewritten to indicate that no benefit with respect to mortality has been shown. Thus, the committee felt that the administration of these agents to treat asymptomatic, nonlife-threatening ventricular arrhythmia should not be a labeling indication for any of these agents. The committee was split regarding appropriate labeling for 1a and 1b agents in patients with symptomatic nonlife-threatening VPCs, or runs of nonsustained ventricular tachycardia, or both. We were unanimous in recommending avoiding labeling that stated that treatment of these arrhythmias with the 1a, 1b agents was contraindicated.

Flecainide: use in supraventricular arrhythmias: The following day, the committee was confronted with the separate and difficult issue of whether flecainide should have a new labeling indication for the treatment of certain types of supraventricular arrhythmias (paroxysmal atrial fibrillation, atrioventricular junctional tachycardias). After hearing a detailed description of the clinical studies presented by the sponsor in support of this application, the committee unanimously felt that there was unequivocal demonstration of efficacy; the key issue was safety. Our recommendation to the FDA was influenced strongly by the CAST, such that we voted approval of a labeling indication for flecainide for the symptomatic, disabling supraventricular arrhythmias (noted above), limited to patients without structural heart disease. Patients with structural heart disease and symptomatic supraventricular arrhythmias require individual consideration of the risk-benefit ratio. Our feeling was that the risk-benefit ratio in patients with supraventricular arrhythmias with structural heart disease was inadequately defined to merit a specific labeling indication.

FDA guidelines for the development of an antiarrhythmic drug: The results of the CAST raise many questions regarding the current FDA guidelines for the development of new antiarrhythmic agents for ventricular arrhythmias. Up to this time, these guidelines have suggested that the following are essential in a viable antiarrhythmic drug development program: defining the antiarrhythmic properties of a specific agent, including the dose-response relations in clinical trials involving patients with chronic stable VPCs; defining whether or not the drug prevents inducibility of sustained ventricular tachycardia using programmed electrical stimulation; clinical trials, generally not placebo-controlled, involving patients with "life-threatening" ventricular arrhythmias; a careful description of the proarrhythmic and negative inotropic effects of the drug, in large measure derived from experience in patients who are at increased risk for arrhythmic death; and a reasonably large experiential database.

The results of the CAST require a careful reassessment of what should be considered adequate to address each of these critical elements. The commitee is sensitive to avoiding excessively strict guidelines that might discourage new drug development; the need for new agents is clearly greater now than ever. The members of the committee realize that it is not realistic to require mortality trials for each antiarrhythmic drug and specific patient population. Many decisions must be made with imperfect data. There was inadequate time for our committee to address changes and clarifications of the specific details of the guidelines; a separate committee meeting will be required.

Public health implications of the CAST: The public health implications of the CAST are emphasized by the timely publication of an analysis of the frequency with which antiarrhythmic agents are being prescribed in this country. Hine et al[8] reported that the use of antiarrhythmic agents in the United States is increasing far out of proportion to the growth of the US population. In fact, from the years 1970 through 1986, they estimated that outpatient antiarrhythmic drug use increased from 3.8 million to 11.5 million new prescriptions annually! It is widely held by pharmaceutical companies that between 40 to 50% of these prescriptions are for the treatment of ventricular arrhythmias. As a result of the CAST, clinicians may change their prescribing habits, especially reconsidering the risk-benefit ratio in patients with potentially lethal ventricular arrhythmias.[1,7]

Until and unless VPC suppression is shown to improve prognosis in the potentially lethal risk group, published studies emphasize an increased risk of antiarrhythmic therapy, not counter-balanced by any demonstrated patient benefit.[1,7] Therefore "routine" prophylactic VPC suppression cannot be recommended. While the results in the encainide/flecainide group of the CAST do not entirely eliminate the VPC suppression hypothesis, neither do they provide any reassurance that this approach is worthwhile. The CAST continues with the additional antiarrhythmic treatment limb, moricizine, representing the electrophysiologic class 1.[1] The results of the moricizine limb will be critically important in determining whether or not the increased risk associated with the use of encainide and flecainide should be generalized to other classes of antiarrhythmic drugs and in further assessing the validity of the VPC suppression hypothesis.

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Cardiac Transplant Hypertension

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Cardiac transplantation is an effective and accepted form of treatment for end-stage heart failure. The growth of heart transplantation has occurred coincident with the introduction of the immunosuppressive agent cyclosporine and subsequent improvement in survival rates. The 1988 registry report of the International Society for Heart Transplantation reported a 79% 5-year actuarial survival for patients treated with cyclosporine.[1] Although rejection and infection account for >50% of deaths after transplant, cardiac etiologies now comprise 25%. Accelerated graft coronary artery disease is a growing concern as long-term survival improves. Also, it is increasingly clear from articles, abstracts and anecdotal reports that rampant, refractory hypertension is a major clinical problem and concern in heart transplant recipients. The goal of this review is to discuss what is known about cardiac transplant hypertension and the threat it may pose to long-term survival.

BACKGROUND AND CLINICAL OBSERVATIONS

Renal function, cyclosporine and hypertension: Traditional immunosuppression regimens for cardiac transplant recipients have included azathioprine and prednisone. In 1981 cyclosporine was introduced and used in combination with lower doses of prednisone ("steroid-sparing effect"). Thompson et al[2] reported in 1983 "the almost universal development of systemic arterial hypertension" in cardiac transplant recipients receiving cyclosporine. Previous reports indicated that <20% of patients receiving azathioprine and prednisone developed postoperative hypertension.[3,4] In 1986 Thompson et al[5] retrospectively compared 18 patients receiving cyclosporine and 12 patients receiving azathioprine. Twelve months postoperatively, the average mean blood pressure was 116 ± 13 and 98 ± 7.5 mm Hg and the serum creatinine was 2.2 ± 0.8 and 1.1 ± 0.2 mg/dl in the cyclosporine and azathioprine groups, respectively.[5] Olivari et al[6] recently reported their observations in 56 patients who received maintenance cyclosporine in addition to azathioprine and prednisone. Despite normal serum creatinine levels at 2 weeks after transplantation, 68% of the patients were hypertensive (>140/90 mm Hg). Six months after transplant, 92% of the patients were hypertensive (requiring treatment) and no correlation was found between blood pressure, serum creatinine or serum cyclosporine levels. Thompson et al[5] reported "the usual demographic characteristics associated with hypertension (age, race, sex, body weight and family history) do not seem to influence the development of postoperative hypertension" after cardiac transplantation. In summary, *virtually all* cyclosporine-treated cardiac transplant recipients develop hypertension soon after surgery, independent of renal impairment and irrespective of conventional risk factors associated with hypertension. Cardiac transplant hypertension is often severe and often inadequately treated despite the use of multiple classes of potent antihypertensive drugs.

Neurohumoral/autonomic: Aberrant neurohumoral function could potentially contribute to the development of hypertension. Levine et al[7] and Olivari et al[8] found plasma norepinephrine levels returned to normal within 6 months after cardiac transplantation despite marked elevation of norepinephrine before transplantation. Thompson et al[6] found that supine and upright renin and 24-hour urinary catecholamines were within normal limits in a group of cyclosporine-treated patients. Bellet et al[9] carefully studied 15 cyclosporine-treated patients while they were not taking antihypertensives and demonstrated no major abnormalities of the renin-angiotensin-aldosterone system. Myers et al[10] elegantly studied a cyclosporine and a noncyclosporine group of cardiac transplant recipients 1 year after surgery. In cyclosporine-treated patients, active renin was significantly lower while the converse was true of inactive renin. Myers et al concluded that long-term cyclosporine therapy may partially block the intrarenal conversion of inactive prorenin to active renin. Numerous investigators have presented preliminary data showing atrial natriuretic peptide levels are elevated in orthotopic cardiac transplant recipients.[11,12] We have reported a resting mean right atrial natriuretic peptide level of 150 ± 92 pg/ml in cardiac transplant recipients (normal <20 pg/ml) and found no correlation between atrial natriuretic peptide and mean arterial pressure.[12]

Reeves et al[13] and subsequently Alexopoulos et al[14] independently have shown an attenuation in heart rate variability in denervated hearts compared to normal ones and a highly significant loss in the usual decrease in heart rate during sleep. Power spectrum analysis has demonstrated that transplant recipients, compared to normal volunteers, showed a 96% reduction in heart rate variability in the 0.02 to 1.0 Hz frequency band, which has been shown to be modulated primarily by the sympathetic nervous system.[15] Yusuf et al,[16] examining the heart rate response to isoprenaline before and after β blockade in cardiac transplant recipients, demon-

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strated an increased sensitivity to β stimulation and speculated that it represented an adaptive mechanism that develops in order to overcome the lack of direct sympathetic nerve stimulation.

It is unknown whether dynamic changes in renal vascular tone are due primarily to effects of cyclosporine or conversely (or in addition) to alterations in renal sympathetic tone related to cardiac transplantation (denervation). Mohanty et al[17] reported cardiopulmonary baroreflex control of forearm vascular resistance was impaired after cardiac transplantation, perhaps secondary to ventricular deafferentation, and hence loss of the "tonic inhibitory influence" on sympathetic outflow to the heart and peripheral circulation originating from the cardiopulmonary region. Importantly, they also examined this reflex in renal transplant recipients receiving cyclosporine to control for its potential effects. However, since the cardiac transplant patients studied were hypertensive and had elevated mean right atrial pressures (14 mm Hg) both factors may have influenced baroreceptor responsiveness. Subsequently, Ellenbogen et al[18] and Smith et al[19] reported the arterial baroreceptor response and heart rate variability (a measure of parasympathetic activity) normalizes after cardiac transplantation. Importantly, they noted failure of these parameters to normalize was correlated with posttransplant hypertension. Thus it does not appear likely that primary abnormalities of baroreceptor function after transplant, which could activate the neurohumoral axis, are the cause of posttransplant hypertension.

Hemodynamics: The cardiac transplant recipient who develops hypertension is characterized by normal cardiac output and abnormally high systemic vascular resistance. Hemodynamics published from 5 transplant centers revealed a mean systemic vascular resistance from 1,306 to 2,150 dynes s cm^{-5}, and a mean arterial pressure from 108 to 121 mm Hg in 159 cyclosporine-treated patients.[5,6,20,21,22] Greenberg et al[20] reported the highest mean arterial pressure (121 mm Hg) and systemic vascular resistance (2,150 dynes s cm^{-5}) and the lowest cardiac index (2.3 liters/m^2), and also observed a modest inverse correlation ($r = -0.47$, $p < 0.01$) between mean aortic pressure and ejection fraction, which we feel is a vitally important observation subsequently discussed in greater detail. After successful cardiac transplantation, right atrial, right ventricular, pulmonary arterial and pulmonary capillary wedge pressures are relatively normal at rest. However, stimuli such as rapid volume expansion, slow deep inspiration or supine bicycle exercise produce abnormalities of right atrial filling waves or striking elevations of the pulmonary capillary wedge pressure.[23–26] Valentine et al[27] reported the presence of a hemodynamic pattern suggestive of restrictive-constrictive physiology in 15% of cardiac allograft recipients. Patients with diastolic dysfunction had impaired systolic performance, but there were no significant differences in either mean arterial pressure or systemic vascular resistance between patients with or without constrictive-restrictive physiology. It is unclear whether cardiac denervation, myocardial pathology (rejection or fibrosis), hypertension, volume overload or pericardial disease explains these hemodynamic observations.

POTENTIAL MECHANISMS OF CARDIAC TRANSPLANT HYPERTENSION

The pathophysiologic mechanisms leading to hypertension in cyclosporine-treated cardiac transplant recipients are unknown. Guilt by association would certainly implicate cyclosporine as a causative factor in cardiac transplant hypertension since the incidence of hypertension in the era before cyclosporine was quite low.

In cyclosporine-induced nephropathy, creatinine is hypersecreted by the renal tubules; thus the enhancement in creatinine clearance over glomerular filtration rate blunts the expected increase in serum creatinine (and decrease in creatinine clearance) as glomerular filtration rate decreases. Serum creatinine is therefore an insensitive marker, and the glomerular filtration rate may be overestimated by the creatinine clearance.[28] Multiple adverse effects of cyclosporine on renal function have been described. They include a reversible, dose-dependent increase in serum creatinine and disproportionate increases in blood urea nitrogen, hyperkalemia, metabolic acidosis, hyperkalemic-hyperchloremic type IV renal tubular acidosis and chronic interstitial nephritis with irreversible renal toxicity.[29,30] The mechanism involved in cyclosporine renal toxicity is unknown but experimental evidence favors the following: tubular toxicity, vasomotor effects of cyclosporine on the renal blood vessels and a specific cyclosporine-associated vascular lesion. Renal histopathology demonstrates both tubulointerstitial and glomerular changes in cyclosporine-treated patients that parallel the degree to which the glomerular filtration rate is depressed. Myers originally proposed that the tubule is the primary site of injury in cyclosporine-associated nephropathy and that the loss of functioning nephrons would favor the development of systemic arterial hypertension, which would then further accelerate the development of glomerulosclerosis.[31] Recently Myers et al[10] reported that "continuous cyclosporine therapy for more than 12 months causes a chronic injury to renal microvessels that is rarely reversible and potentially progressive." In this controlled study comparing cyclosporine- and noncyclosporine-treated patients, important differences were observed in the cyclosporine-treated patients: significant elevation of renal vascular resistance, proteinuria, arterial hypertension, abnormalities of prorenin to renin conversion and renal histopathologic changes. Murray et al[30] examined the effect of cyclosporine on renal hemodynamics in conscious rats and made a series of provocative and clinically relevant observations. An infusion of cyclosporine resulted in a significant decrease in renal blood flow, an increase in renal vascular resistance, stimulation of plasma renin activity and increased urinary 6-keto-PGF1-α excretion. Pretreatment with captopril did not prevent the decrease in renal blood flow, suggesting angiotensin II was not the mediator of cyclosporine-induced vasoconstriction. Administration of a nonsteroidal antiin-

TABLE I Hemodynamics After Cardiac Transplantation

Center (Ref.)	Pts (n)	MAP (mm Hg)	SVR (dynes s cm^{-5})	CI (liters/min/m^2)	CO (liters/min)
Minnesota[6]	56	108	1,963	—	4.9
Paris[22]	28	114	1,306	4.1	—
Palo Alto[10]	37	115	1,614	—	5.7
Columbus*	20	115	1,838	2.7	5.1
Pittsburgh[20]	18	121	2,150	2.3	—

* unpublished observation.
CI = cardiac index; CO = cardiac output; MAP = mean arterial pressure; SVR = systemic vascular resistance.

flammatory agent augmented cyclosporine-induced vasoconstriction, suggesting a protective effect of prostaglandins. Renal denervation or administration of phenoxybenzamine "dramatically reduced" the decrease in renal blood flow after cyclosporine administration. They concluded that "cyclosporine causes renal vasoconstriction which is mediated by the renal sympathetic nervous system, and that vasoconstriction is exacerbated by the administration of cyclooxygenase inhibitors."[30] Cyclosporine also appears causally related to the development of hypertension in humans who have not received transplants (e.g., rheumatoid arthritis) and in recipients of nonrenal or noncardiac transplants.

Corticosteroids have been implicated in the pathogenesis of cardiac transplant hypertension. Intuitively it has been proposed that cardiac transplant hypertension is due to a mineralocorticoid effect producing a volume overload state and systemic arterial hypertension. The presence of normal intracardiac filling pressures and cardiac output in the face of hypertension does not support the premise of "volume overload"-related hypertension. The fact that hypertension is universal and rampant in patients receiving cyclosporine-based triple immunosuppression ("steroid-sparing regimen") versus uncommon and mild in patients receiving azathioprine and prednisone further suggests corticosteroids play a minor role, if at all, in the pathogenesis of cardiac transplant hypertension.

No definite neurohumoral abnormalities have been identified in cardiac transplant recipients that appear related to the pathogenesis of cardiac transplant hypertension. Virtually all clinical studies have concluded the renin-aldosterone-angiotensin axis is normal under baseline conditions, and captopril does not alter renal hemodynamics either experimentally or clinically. Arterial baroreceptor function recovers after transplantation but the development of abnormal baroreceptor sensitivity is related to systolic hypertension.[18]

At the time of transplantation the donor heart is immediately faced with a high impedance state due to residual peripheral vasoconstriction and potential mismatching in impedance between the donor denervated heart and the recipient vasculature.[22] This is relevant, in that Nichols et al[32] examined the interrelation between aortic input impedance and left ventricular performance with age, and concluded that an increase in vascular load may account for the observed decrease in stroke volume and development of mild left ventricular hypertrophy observed with advancing age. The cardiac transplant recipient potentially represents an extreme example of mismatching between the native vasculature and the transplanted left ventricle. Posttransplant systemic arterial hypertension, cross-sectional area of the recipient peripheral vascular bed and stiffness of the recipient aorta appear to be important variables related to ventricular/vascular coupling and ultimately left ventricular function. Perhaps more importantly, no autonomic feedback or communication exists between the peripheral and central circulation in orthotopic cardiac transplant recipients, and the heart is unable to respond to changes in afterload by alterations in inotropic state normally mediated via sympathetic innervation. The denervated heart does not recognize or synthesize input from the peripheral circulation, and continues to contract vigorously and eventually hypertrophy. This scenario may, in part, explain why the usual hemodynamic profile after transplantation is characterized by increased systemic vascular resistance, normal cardiac output, and normal ejection fraction. Why the systemic vascular resistance remains elevated in the face of normal cardiac function is unknown, but may be an independent variable related to direct vascular effects of cyclosporine or cyclosporine-associated ablative nephropathy as previously discussed. Whether ventricular/vascular uncoupling plays a primary role in the pathogenesis of cardiac transplant hypertension is unclear; however, the dire implications of systemic arterial hypertension after transplantation are unequivocal and will be subsequently discussed.

TREATMENT OF CARDIAC TRANSPLANT HYPERTENSION

There are no peer-reviewed published clinical trials examining the effectiveness of pharmacologic strategies in the treatment of cardiac transplant hypertension. Our experience, anecdotal reports and personal communications with transplant physicians from major centers indicate cardiac transplantation hypertension is often refractory, and optimal control is difficult to achieve despite the use of multiple, potent antihypertensives. Meticulous attention to immunosuppression and assiduous efforts to use the lowest possible doses of cyclosporine and steroids while still preventing rejection are imperative and crucial cornerstones of therapy. Conventional practice advises that cyclosporine be maintained at higher doses the first 6 to 12 months after surgery. Unfortunately the nephrotoxic effects of cyclosporine appear to be cumulative and may in effect "set the stage" for longstanding hypertension that persists even after cyclosporine doses are ultimately reduced. As the mechanism of cardiac transplant hypertension is purely conjectural at present, our caution regarding the use and amount of cyclosporine is speculative. It is our impression that in the early postoperative period dynamic changes in renal function and blood pressure may more closely correlate with cyclosporine dosing. In contrast, in the late postoperative period, adjustments in cyclosporine doses have little influence on blood pressure.

Our clinical impression is consistent with data showing that withdrawal of cyclosporine after a few months of therapy was followed by an increase in renal plasma flow, whereas renal vascular resistance remained elevated in patients withdrawn from cyclosporine between 36 and 48 months after institution of therapy.[10]

Angermann et al[33] prospectively treated 10 hypertensive cardiac transplant recipients with enalapril and furosemide alone or in combination with verapamil and documented that very effective blood pressure control was achieved over 5.7 months of follow-up. Although a small number of patients were examined, this remains the only prospective study that carefully examined the efficacy of any antihypertensive regimen in cyclosporine-treated cardiac transplant recipients.

Many classes of antihypertensive agents have been used in the treatment of cardiac transplant hypertension, and our experience and recommendations concerning each group of drugs will be briefly discussed. Diuretics should be used cautiously because the balance between edema/hypertension and volume depletion/hypotension can be tenuous in a subset of these patients. Overzealous diuresis can potentiate the apparent nephrotoxicity of cyclosporine by further reducing renal blood flow and altering cyclosporine pharmacokinetics. We have observed striking dynamic changes in blood urea nitrogen and serum creatinine that occurred over a 24- to 48-hour period related to the state of hydration. The use of diuretics is probably justified in cardiac transplant hypertension because an increase in plasma volume has been described in cyclosporine-treated patients and may relate to cyclosporine-associated sodium retention as demonstrated in renal allograft recipients. No studies have been published examining the antihypertensive or renal effects of β blockers in cardiac transplant recipients. The effectiveness of calcium antagonists has not been tested in a randomized, controlled clinical trial. Calcium antagonists alter cyclosporine metabolism and have the potential to elevate cyclosporine levels, which may negate any salutary antihypertensive effect by precipitating renal dysfunction. Renal function and cyclosporine levels should be carefully monitored when calcium antagonists and cyclosporine are administered concurrently. The renin-angiotensin axis appears normal in cyclosporine-treated cardiac transplant recipients. Experimental data, as previously discussed, demonstrate that the cyclosporine-induced renal vascular effects are not reversed by captopril. Potential problems regarding the additive renal toxicity of angiotensin converting enzyme inhibitors and cyclosporine have not been observed clinically. Reversible proteinuria and renal dysfunction associated with angiotensin converting enzyme inhibitors has not been reported in either renal or cardiac transplant recipients. Angermann's preliminary data suggest additional clinical trials should be performed to examine the antihypertensive efficacy of enalapril as monotherapy or in combination with verapamil. We and others have used hydralazine in combination with a diuretic in the initial management of cardiac transplant hypertension. Many patients require 400 mg/day of hydralazine, which has been well tolerated both short and long term. In more refractory cases, the addition of minoxidil is sometimes necessary to achieve blood pressure control. Clonidine has been well tolerated in our patient population. Based on the previously discussed observations made in rats, it is attractive to postulate that clonidine may ameliorate hypertension by augmenting renal blood flow in cyclosporine-treated patients. Our experience with the use of prazosin is limited and we have not used α-methyldopa in cardiac transplant patients. We are unaware of any reports describing the clinical usefulness of other sympatholytic agents for cardiac transplant hypertension.

Based on our experience, we believe nonsteroidal antiinflammatory agents should be avoided in patients receiving cyclosporine. Blood urea nitrogen and serum creatinine increase precipitously within 24 to 48 hours after introducton of nonsteroidal antiinflammatory agents, but fortunately the renal dysfunction is rapidly reversible after withdrawal. This clinical observation in humans relates nicely to the observation of Murray et al[30] that meclofenamate potentiates the renal vasoconstrictive action of cyclosporine in rats. Aspirin, nonsteroidal antiinflammatory agents, or potentially any prostaglandin inhibitor may potentiate cyclosporine induced renal disease and cardiac transplant hypertension. The use of these drugs in cyclosporine treated patients should be further investigated.

The observations that cardiac transplant recipients lack the normal nocturnal decrease in blood pressure and that the early morning blood pressure is often the highest measurement help the clinician tailor antihypertensive therapy. Optimal blood pressure management is often achieved by preferentially giving larger doses of antihypertensives at bedtime so as to target treatment for the specific time of day when blood pressure is typically highest. Afternoon blood pressures are often much lower than morning measurements, and if the same dose of vasodilator is given consistently, symptomatic, iatrogenic hypotension can occur.

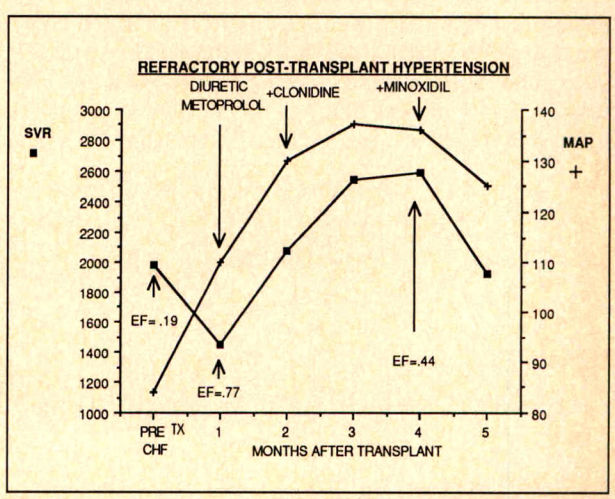


FIGURE 1. The course of the blood pressure and hemodynamic changes in a cyclosporine-treated cardiac transplant recipient are shown over time. EF = ejection fraction; MAP = mean arterial pressure (mm Hg); SVR = systemic vascular resistance (dynes s cm^{-5}).

IMPLICATIONS

The universal occurrence of hypertension and its refractory nature in essence give every transplant recipient taking cyclosporine a new cardiovascular disease in substitution for the disease (end-stage heart failure) that was "cured." It has been our observation that patients with poorly controlled hypertension often complain of fatigue and exertional dyspnea despite well-preserved ventricular systolic function. We believe there is an exceedingly important and close link between blood pressure and ventricular function in cardiac transplant recipients intimately related to long-term morbidity and survival.

The concept of ventricular/vascular uncoupling was introduced and previously discussed. The majority of evidence suggests cardiac transplant hypertension is cyclosporine-associated and transplantation or denervation alone do not explain the pathogenesis of hypertension. However, denervation and ventricular/vascular uncoupling combined with cyclosporine-associated severe hypertension may represent an extremely pathologic combination. Table I lists the hemodynamics for 159 cyclosporine-treated patients and shows a tendency toward a reduction in cardiac output accompanying an increase in systemic vascular resistance. We have observed a close relation between blood pressure and ventricular function in many of our cardiac transplant recipients. Figure 1 shows the typical and striking changes in mean arterial pressure and systemic vascular resistance in a 49-year-old male cardiac transplant recipient receiving cyclosporine. The mean arterial pressure and systemic vascular resistance increase progressively despite cumulative addition of several classes of antihypertensives. As the afterload increases, the left ventricular ejection fraction declines from an excellent value 1 month after surgery, 77%, to 44% when the systemic vascular resistance is 2,433 dynes s cm^{-5}. Endomyocardial biopsies obtained when radionuclide angiographic ejection fraction was measured were free of rejection.

Compensatory hypertrophy is a normal adaptive response to cardiovascular disease. In the presence of hypertension, hypertrophy slowly develops as hypertension worsens. Normally, cardiac and extracardiac compensatory factors are activated to reduce the load on the heart and delay the appearance of overt heart failure. It is unlikely that all these reflexes are activated in the denervated, transplanted heart. The transplanted heart, when placed in a high afterload circulation (hypertension), with an intrinsically high heart rate due to denervation and with it stripped of its normal compensatory mechanisms, may represent an in vivo experimental model of the progression of hypertrophy leading to cardiac failure (Figure 2). As such, it is a condensed version of the "Meerson hypothesis" of hypertrophy and failure.[34] Borow et al[35] noninvasively determined load independent indexes to identify preclinical left ventricular dysfunction in cardiac transplant recipients. They reported left ventricular wall mass and end-diastolic wall thickness is greater in transplant recipients, and they also concluded it represented a normal physiologic response to increased systemic vascular resistance, peak systolic pressure and peak systolic wall stress.[35] Other investigators have expressed concern over the apparent relation between systemic arterial hypertension and left ventricular systolic and diastolic function.[20,22] However, this issue has not been examined in a systematic, prospective fashion.

MANDATE FOR THE FUTURE

A number of issues are uninvestigated, and important questions remain unanswered regarding the etiology, pathophysiology and treatment of cardiac transplant hypertension. Cognizance of the lack of knowledge related to this problem, which poses a threat to the long-term effectiveness of the only successful treatment for end-stage heart failure, requires mandates for the future: better characterization of the pathophysiology of postcardiac transplant hypertension so that rational approaches to therapy can be developed; determination of the minimally effective dose of cyclosporine from the standpoint of immunosuppression and its cumulative toxicity, time course and reversibility of nephrotoxicity, as well as its relation to hypertension; determination of the relation between steroid use/dosage and cardiac transplant hypertension; establishment of the goals of antihypertensive therapy for cardiac transplant hypertension (currently it is assumed a reduction in cardiovascular morbidity and mortality analogous to that seen in native hypertension can be achieved with the 140/90 mm Hg benchmark); additional insight into the concept

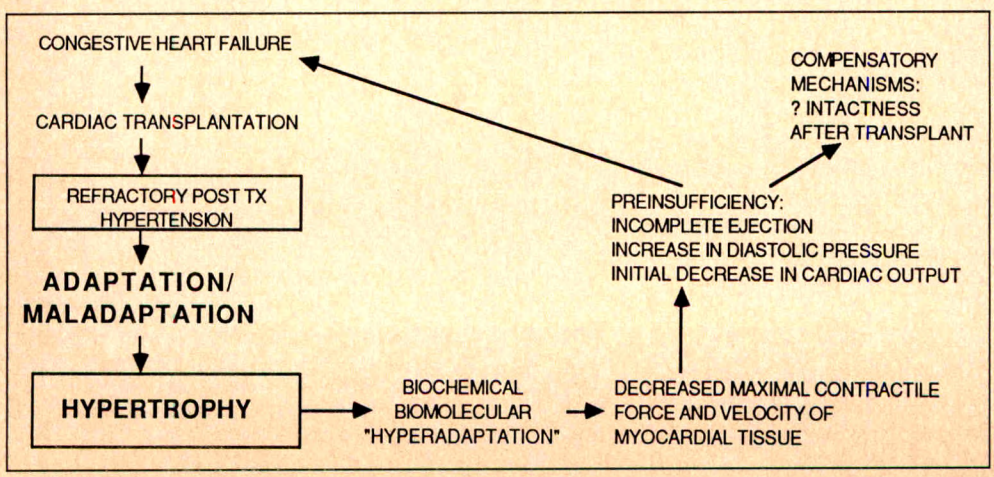


FIGURE 2. Proposed schematic application of the Meerson hypothesis to severe, refractory hypertension after cardiac transplantation.

of ventricular/vascular uncoupling and the risk posed by hypertension to the denervated, "unprotected" heart, and the importance of vigilant blood pressure surveillance; multicenter trials (due to the limited number of patients) to test the efficacy of antihypertensive drugs showing promise in the treatment of cardiac transplant hypertension; and avoiding overinterpretation of post-cardiac transplant physiologic studies that do not account, or control, for the presence or absence of cardiac transplant hypertension.

We firmly believe that long-term morbidity and mortality are, in part, related to cyclosporine-associated hypertension. Both subtle and frank abnormalities of diastolic and systolic function are related to and magnified by uncontrolled hypertension. Physicians caring for cardiac transplant recipients should be vigilant and diligent in the surveillance and treatment of cardiac transplant hypertension.

Acknowledgment: We sincerely thank our colleague, Dr. P. David Myerowitz, whose dedication to the Ohio State University Heart Transplant Program made this article possible.

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Lessons from the Past and Reflections on the Cardiac Arrhythmia Suppression Trial

Stephen C. Vlay, MD

We still do not know how to treat ventricular premature complexes (VPCs) in most patients. There is agreement among most (unfortunately not all) cardiologists that survivors of sustained ventricular tachycardia (VT) or sudden cardiac arrest not associated with the acute phase of myocardial infarction deserve intensive evaluation including electrophysiologic testing in most. Cautions urged 7 years ago as well as pharmacotherapeutic guidelines remain valid.[1]

Treating patients inappropriately (or even for appropriate indications) with type 1 antiarrhythmic drugs may worsen a native arrhythmia and cause sudden cardiac death.

The type 1c agents including flecainide and encainide may be among the most proarrhythmic in patients with coronary artery disease and prior myocardial infarction. Not enough data are available on propafenone to condemn it, and it must be remembered that it is different pharmacologically (possessing mild β-blocker activity).

One must be aware of the formidable influence of pharmaceutical industry advertising. Witness the marketing efforts of the past few years in which the virtues of treating VPCs with flecainide or encainide were extolled ad nauseum. (Physicians, in fact, are now paying the price: many patients started on flecainide or encainide therapy who heard the results of the Cardiac Arrhythmia Suppression Trial [CAST] have called the prescribing physician and demanded cessation of the drug or a lengthy explanation.)

Data cannot and should not be extrapolated from 1 patient population to another. We[2] described a more favorable outcome in survivors of symptomatic VT or ventricular fibrillation after intensive evaluation and therapy when nonsustained VT was also eradicated from the ambulatory electrocardiographic recording. Although it would seem to follow that abolishing this arrhythmia from other groups would also be beneficial, the data from CAST indicate the error in this extrapolation (a higher incidence of sudden death with flecainide or encainide).[3]

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Similarly, we must not damn the utility of flecainide or encainide in other populations such as patients with paroxysmal atrial or preexcitation arrhythmias. In patients with normal left ventricular function without myocardial ischemia, these drugs may be quite effective and well tolerated. Nevertheless, a recent report[4] of 3 patients also indicated the potential for ventricular proarrhythmias. Consequently, more study, but not hysteria, is necessary to learn if there is a role for these drugs.

The terms malignant, potentially malignant and benign have been advocated and used freely. I have no problem with the terms benign and malignant but potentially malignant seems to "potentially" cause confusion in the evaluation and treatment of patients with arrhythmias. When does one say that the 3-beat salvo of nonsustained VT in a patient with coronary artery disease really is benign and requires only a β blocker? When is it really a harbinger of a lethal episode in the near future that might be avoided with electrophysiologic-guided therapy? Problems with terminology also undermine our ability to accurately stratify patients' risks when ventricular ectopic activity—not malignant or benign arrhythmias at the ends of the spectrum—is present.

In short, if one is concerned about the use of type 1 antiarrhythmic drugs in asymptomatic patients with serious underlying heart disease, it may be better to avoid them. Other strategies may include the use of β blockers if drug therapy is still considered desirable, if there are no contraindications and particularly if there is another reason to give the drug (such as ischemia after myocardial infarction).

Risk stratification may be enhanced through the use of signal averaging. Late potentials may indicate a higher risk of sudden cardiac death. Together with an estimation of the severity of the underlying left ventricular dysfunction, this scheme may assist in the decision to recommend electrophysiologic testing. One cannot send all patients to the electrophysiologic laboratory, but perhaps not enough undergo this predictive study when the risk of sudden death with the casual use of type 1 antiarrhythmic drugs is considered. The manner in which the preliminary results of CAST were released deserves comment, if not criticism. Certainly there was an obligation to stop the study and report the adverse events related to flecainide and encainide. Unfortunately, the public received the message via the mass media and their reaction was almost hysterical: patients stopping their drugs without calling their physicians; pharmacists

telling their patients that the drug prescribed was dangerous; patients needlessly worried about risks that they themselves did not face; physicians besieged by phone calls; and patients losing confidence in their physicians. At no point was the public reassured that the results pertained to a specific patient population, that results could not be extrapolated to other groups, that patients whose therapy had been guided by electrophysiology testing were at little risk of proarrhythmia or that patients should discuss the matter with their physician but not be unduly alarmed.

Currently we have nationwide programs raising awareness of problems with elevated serum cholesterol, the risk of hypertension, the danger of smoking and the need to consult a physician when experiencing chest pain. The article by Morganroth et al in this issue of *The American Journal of Cardiology* indicates that 33 to 43% of cardiologists thought it appropriate to prescribe amiodarone for refractory benign or potentially malignant arrhythmias. In addition, 60% thought it appropriate to use encainide or flecainide as initial therapy for malignant ventricular arrhythmias. Personally I hope that they misread the questionnaire and meant to give a different answer. Physicians must also be reminded that there is a difference between eradicating ventricular ectopy on the ambulatory electrocardiogram and preventing sudden cardiac death.

Five years ago, I recommended that a panel of arrhythmia specialists be convened to discuss indications for evaluation and treatment of ventricular ectopic activity.[5] Perhaps that idea should now come to fruition. Certainly we need a physician awareness program to combat the apparent incomplete understanding of the potential risks of treatment as well as the pharmacology and toxicity of antiarrhythmic drugs. It is even possible that these efforts could be partially supported by the pharmaceutical industry, but in a nonpartisan way.

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Percutaneous Transluminal Coronary Angioplasty for Silent Myocardial Ischemia

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In the 13 years since the first percutaneous transluminal coronary angioplasty (PTCA) was performed,[1] the number of procedures performed has increased dramatically. This in part relates to a greater availability of the procedure to patients with coronary artery disease as the number of operators has increased, but it also reflects an expansion of the indications for PTCA.[2] The indications for any therapeutic intervention should be based on its potential benefits, the likelihood of success, the frequency of complications and the subsequent morbidity and mortality. A comparison of earlier and more recent series of patients undergoing PTCA has documented an increase in success rate and a decrease in complication rate.[3] The only proven benefit of PTCA, however, remains the relief of symptomatic myocardial ischemia. Whether PTCA also favorably alters the risk of subsequent myocardial infarction or death in patients with symptomatic ischemia can only be inferred from a comparison of studies of outcomes in patients undergoing PTCA with other studies of patients who have been treated with medical therapy. There have been no randomized studies comparing outcomes in patients with angina treated medically versus those undergoing PTCA. Because of its efficacy in relieving angina, however, PTCA has become a widely accepted alternative to surgical and medical therapy in symptomatic patients with 1- or multivessel coronary artery disease.

The role of PTCA in asymptomatic patients remains poorly defined. Because this group of patients will not have any immediate symptomatic benefit from PTCA, the indication for PTCA must be based on its impact on subsequent morbidity and mortality. Several studies have demonstrated that patients with coronary artery disease have an increased risk of myocardial infarction or death if they have evidence of inducible or spontaneous myocardial ischemia whether or not ischemia is associated with pain.[4,5] The extent and location of the coronary narrowing, the presence and severity of left ventricular dysfunction, the level of exercise achieved on the treadmill and the extent of ischemia at peak exercise are generally accepted as predictors of outcome whether or not the patient is symptomatic.[6] Thus, patients with silent myocardial ischemia, excellent exercise capacity, 1-vessel coronary artery disease and normal left ventricular function have an excellent long-term prognosis while similarly asymptomatic patients with 3-vessel coronary disease, depressed left ventricular function and poor exercise capacity will have a relatively high risk of subsequent myocardial infarction or death. Although it is clear that a subgroup of patients with asymptomatic myocardial ischemia will benefit from surgical revascularization (i.e., those with 3-vessel coronary disease and left ventricular dysfunction and those with left main coronary stenosis) it is unclear which, if any, asymptomatic patients will benefit from PTCA.

In the present issue of the *Journal*, Anderson et al[7] report the long-term outcome of 114 patients who underwent PTCA and never had angina pectoris or myocardial infarction. These 114 patients represent <2% of all patients who underwent PTCA at their institution between 1980 and 1987. This low percentage presumably reflects not only the relatively small number of entirely asymptomatic patients who undergo cardiac catheterization but also the reluctance of patients and physicians to proceed with revascularization without the prospect of immediate symptomatic benefit and with no clear evidence of long-term benefit on morbidity and mortality. The study population consisted predominantly of patients with 1-vessel disease (69%) and normal left ventricular function. Such patients in general have a good prognosis without revascularization. Presumably a subgroup of these patients were at a higher risk of subsequent cardiac events because of a markedly positive exercise tolerance test but no information is provided regarding the extent of ischemia during stress testing or the level of exercise at which the ischemia occurred. Of the 114 patients, 7 (6%) sustained a myocardial infarction either during PTCA (2 patients) or during the mean follow-up period of 43 months (5 patients). There were no deaths. Previous studies of untreated or medically treated asymptomatic patients with significant coronary artery disease have reported a similar frequency of myocardial infarction. In 1 study of 78 asymptomatic men with positive stress tests and angiographically proven coronary artery disease, 4 (5.1%) sustained a myocardial infarction during a mean follow-up period of 57 months and 2 (2.6%) died.[8,9] In another study of 50 asymptomatic men with coronary artery disease, 7 (14%) had a myocardial infarction and 3 (6%) died during an 8-year follow-up period.[10] The absence of mortality over a follow-up period ranging from 5 to 92 months in the present study supports the safety of a "PTCA approach" to asymptomatic patients, but only a

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very large randomized trial would be able to detect a reduction in mortality in this very low risk population, which has a ≤0.5% annual mortality without intervention.

One of the difficulties associated with performing PTCA in asymptomatic patients is the detection of restenosis. Although it is well established that restenosis usually presents as recurrent angina, not myocardial infarction or sudden death, the asymptomatic patient could develop recurrent ischemia without symptoms and then progress, without warning, to myocardial infarction or sudden death. The low frequency of myocardial infarction and death during the follow-up period in the study by Anderson et al is reassuring in this regard. In patients who have undergone PTCA for silent myocardial ischemia, however, it would seem prudent to recommend frequent stress testing particularly during the first 6 months after PTCA so that restenosis could be diagnosed and treated early before the patient progressed to a more severe manifestation of restenosis.

Although the study by Anderson et al in this issue of the *Journal* supports the safety of PTCA in asymptomatic patients without a history of angina or myocardial infarction, it does not define the overall role of PTCA in this population. Until the impact of medical therapy, PTCA and surgery on the prognosis of asymptomatic patients is defined by randomized trials, PTCA in this population should be limited to patients with suitable coronary anatomy[3] who are at a high risk of subsequent morbidity and mortality because of clear evidence of severe but silent myocardial ischemia at a low workload on stress testing.

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Some Good Cardiologic Books Published in 1989

Books, books, books! Some of the nonmedical ones in 1989 included Nancy Reagan's *My Turn: The Memoirs of Nancy Reagan;* former attorney general Ed Meese's *Witness to History: Power and Politics in the Reagan White House;* Robert Bork's *The Tempting of America: The Political Seduction of the Law;* John Barry's *The Ambition and the Power: The Fall of Jim Wright;* Norman Cousins' *Head First: The Biology of Hope;* Bill McKibben's *The End of Nature;* Stephen Jay Gould's *Wonderful Life: The Burgess Shale and the Nature of History;* Gore Vidal's *Hollywood;* James Michener's *Caribbean;* Carey Roberts' *Touch a Cold Door;* 4 books on Richard Nixon; at least 12 new books on World War II; and of course many others. More cardiologic books appeared in 1989 than in 1988. The average cost of a cardiologic book in 1989 was $65.00. This piece will mention some good cardiologic books appearing in 1989.

1. Hurst JW, Editor in Chief, Schlant RC, Associate Editor. *The Heart, Arteries and Veins*. New York: McGraw-Hill Information Services Co., 1990:2,348, $99.00 (single volume), $115.00 (double volume).

2. Julian DG, Camm AJ, Fox KM, Hall RJC, and Poole-Wilson PA, editors. *Diseases of the Heart*. London: Bailliere Tindall, 1989:1,709, $125.00.

The Hurst book is a must for a cardiologic library. It actually complements the Braunwald book in that it has a bit more on therapy and a bit less on diagnosis and pathophysiology, the opposite of the Braunwald book. The Hurst book is less expensive and contains much more information than does the Julian book.

3. Long WA, editor. *Fetal and Neonatal Cardiology*. Philadelphia: WB Saunders Co., 1990:863, $195.00.

I suspect that this book will rapidly become the bible on this subject.

4. Adams FH, Emmanouilides GC, Riemenschneider TA, editors. *Moss' Heart Disease in Infants, Children, and Adolescents*, Fourth edition. Baltimore: Williams & Wilkins, 1989:1,066, $149.95.

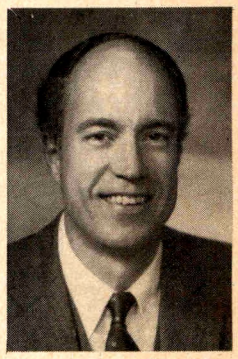
This excellent book by 73 contributors includes nearly all forms of cardiac disease in the young. Exactly 50% of the text concerns congenital defects; the other 50% concerns acquired heart diseases, procedures and special problems.

5. Elkayam U, Gleicher N, editors. *Cardiac Problems in Pregnancy. Diagnosis and Management of Maternal and Fetal Disease*. New York: Alan R. Liss, Inc., 1990:809, $124.50.

A comprehensive book on this subject.

6. Gazes PC. *Clinical Cardiology*. Philadelphia: Lea & Febiger, 1990:594, $55.00.

This easily readable book presents in a simple, concise manner nonencyclopedic cardiologic information useful in everyday practice. This book is a good one for noncardiologists seeking cardiologic information.



7. Opie LH. *Clinical Use of Calcium Channel Antagonist Drugs*. Boston: Kluwer Academic Publishers, 1989:304, $80.00.

An excellent book.

8. Williams R. *The Trusting Heart. Great News About Type A Behavior*. New York: *Times* BOOKS, 1989:240, $17.95.

Dr. Williams is director of the Behavioral Medicine Research Center at Duke University. He has linked certain kinds of type A behavior, such as hostility and rage, with cardiac disease, and he maintains that these harmful traits can be separated from positive aspects of type A personality such as ambition, high energy and enthusiasm, thereby rendering the type A person even healthier than the placid type B counterpart.

9. Francis GS, Alpert JS, editors. *Modern Coronary Care*. Boston: Little, Brown and Co., 1990:797, $95.00.

This book by an array of distinguished cardiologists provides a huge amount of information on acute myocardial infarction and how to manage it.

10. Julian DG, Kubler W, Norris RM, Swan HJ, Collen D, Verstraete M, editors. *Thrombolysis in Cardiovascular Disease*. New York: Marcel Dekker, 1989:460, $79.75.

A fine update on a rapidly changing topic.

11. Franklin BA, Gordon S, Timmis GC, editors. *Exercise in Modern Medicine*. Baltimore: Williams & Wilkins, 1989:300, $42.95.

Although there are numerous books on exercise testing and training for presumably healthy adults and cardiac patients, this one is comprehensive and includes requirements of special patient populations such as those with peripheral vascular disease, diabetes mellitus, end-stage renal disease, severe obesity, chronic obstructive pulmonary disease, asthma, cystic fibrosis, healthy elderly subjects, wheel chair-dependent patients and pregnancy.

12. Pepine CJ, Hill JA, Lambert CR, editors. *Diagnostic and Therapeutic Cardiac Catheterization*. Baltimore: Williams & Wilkins, 1989:612, $69.50.

13. Miller G. *Invasive Investigation of the Heart. A Guide to Cardiac Cathertisation and Related Procedures*. Oxford: Blackwell Scientific Publications, 1989:496, $160.00.

14. Leachman DR, Leachman RD. *Coronary and Peripheral Angiography and Angioplasty*. Philadelphia: JB Lippincott, 1989:149, $34.50.

Although the Miller book is beautifully prepared, its cost is prohibitive (because it was published abroad). The Pepine book is superb, fully packed, and very reasonable in view of its 612 pages, 19% more than in the Miller book. It will give the Grossman book (1986, third edition)

on this subject a run for its money. The Pepine book has 180 pages on specific clinical states, and their assessment and intervention by catheter techniques. The book discusses how noninvasive data and results of clinical trials may supplement or replace catheterization. One chapter deals with radiographic contrast agents. This book should be useful both to those who do catheterizations and to those who refer patients for these procedures. The Leachman father-and-son book is a handy practical guide.

15. Topol EJ, editor. *Textbook of Interventional Cardiology*. Philadelphia: WB Saunders Co., 1990:954, $95.00.

16. Kapoor AS, editor. *Interventional Cardiology*. New York: Springer-Verlag, 1989:415, $99.00.

Two books of nearly similar price but the Topol book contains over twice the amount of information as the Kapoor book. The Topol book is the best so far on this rapidly changing subject.

17. Schoen FJ. *Interventional and Surgical Cardiovascular Pathology. Clinical Correlations and Basic Principles*. Philadelphia: WB Saunders, 1989:410, $82.35.

This good book focuses on morphologic features of hearts that had been subjected to interventional (operative or nonoperative) procedures. It contains 3,267 references in its 9 chapters, all but 1 of which is written by Schoen.

18. Laragh JH, Brenner BM, editors. *Hypertension, Pathophysiology, Diagnosis, and Management*. Volumes I and II, New York: Raven Press, 1990:2,436, $295.00.

Almost surely this is the most comprehensive book published on systemic hypertension. If it is not in these 2 volumes, the information must not be available.

19. Schamroth L. *The 12 Lead Electrocardiogram*. In 2 books. Oxford: Blackwell Scientific Publications, 1989:848, $199.00.

20. Dunn MI, Lipman BS. *Lipman-Massie Clinical Electrocardiography*. Eighth edition. Chicago: Year Book Medical Publishers, Inc., 1989:620, $64.95.

21. Fisch C. *Electrocardiography of Arrhythmias*. Philadelphia: Lea & Febiger, 1990:451, $49.50.

Schamroth's comprehensive texts deal exclusively with 12-lead contour analysis and do not include abnormal heart rhythms. It is the magnum opus of the late Leo Schamroth. It is divided in 4 major divisions: genesis of the normal and abnormal electrocardiogram; acquired heart disease; congenital and hereditary heart disease; and electrocardiographic case studies. The latter constitute most of book 2.

The Dunn-Lipman book began in 1951 as *Clinical Unipolar Electrocardiography*. The present title is the fourth this book has carried. This edition is the first to have references after each chapter. This book reminds me of Grant's wonderful electrocardiography book published in the 1950s.

Charles Fisch has focused his professional life on the electrocardiography of arrhythmias, and taught this subject to literally thousands of physicians. His long overdue book, which encompasses nearly all arrhythmias, focuses on mechanisms and electrocardiographic concepts rather than definition and classification. It includes 451 figures, and nearly all are electrocardiographic tracings recorded from the body's surface. The tracings and their explanations are the essence of this fine book.

22. St. John Sutton M, Oldershaw PJ, editors. *Textbook of Adult and Pediatric Echocardiography and Doppler*. Boston: Blackwell Scientific Publications, 1989:880, $110.00.

23. Hagan AD, DeMaria AN. *Clinical Applications of Two-Dimensional Echocardiography and Cardiac Doppler*, Second edition. Boston: Little, Brown and Company, 1989:556, $75.00.

24. Schapira JN, Harold JG, editors. *Two-Dimensional Echocardiography and Cardiac Doppler*, Second edition. Baltimore: Williams & Wilkins, 1990:670, $99.50.

25. Atlee JL III. *Perioperative Cardiac Dysrhythmias: Mechanisms, Recognition, Management*, Second edition. Chicago: Year Book, 1990:443, $69.95.

The St. John Sutton book is comprehensive and contains much information for the money. On the other hand, it includes both congenital and acquired heart diseases, and those interested in one may not be so interested in the other. The Hagan and DeMaria book also is of high quality. The Atlee book, written by an anesthesiologist, focuses on cardiac arrhythmias occurring in the operating room or recovery room or in the surgical intensive care unit. This book could use more illustrations.

26. Nanda NC. *Atlas of Color Doppler Echocardiography*. Philadelphia: Lea & Febiger, 1989:544, $135.00.

27. Nanda NC, editor. *Textbook of Color Doppler Echocardiography*. Philadelphia: Lea & Febiger, 1989:359, $110.00.

28. Gura GM Jr. *Video Atlas of Two-Dimensional Color Flow Doppler Echocardiography*. Boston: Little, Brown and Co., 1989:180, $250.00.

29. Maurer G, Mohl W, editors. *Echocardiography and Doppler in Cardiac Surgery*. New York: Igaku-Shoin, 1989:355, $97.50.

The Nanda *Atlas* encompasses Nanda's experience with Doppler flow imaging for nearly 5 years. The various types of flow patterns seen in both acquired and congenital cardiac disease are seen in over 1,600 anatomic and color Doppler illustrations and they represent the most detailed, definitive and comprehensive work in this field to date. The *Textbook* is a companion to the *Atlas*. It includes 32 chapters and an appendix written by well-recognized authorities. A *Video Tape of Color Doppler Echocardiography* of about 2 hours length was also prepared by Nanda to supplement both the *Atlas* and the *Textbook*.

The Gura and accompanying 2 videos occupying 2.5 hours feature 50 case studies. The excellent color prints are shown in more detail in video.

30. Erbel R, Khandheria BK, Brennecke R, Meyer J, Seward JB, Tajik AJ, editors. *Transesophageal Echocardiography. A New Window to the Heart*. Berlin: Springler-Verlag, 1989:360, $112.50.

CENTRAL LIBRARY

This book comprises proceedings of a symposium. Methods, technique, anatomic correlation and future applications are discussed by recognized experts. The book is overpriced and disappointing.

31. Gray RJ, Matloff JM, editors. *Medical Management of the Cardiac Surgical Patient*. Baltimore: Williams & Wilkins, 1990:378, $52.95.

32. Bojar RM with Murphy RE, Payne DD, Diehl JT. *Manual of Perioperative Care in Cardiac and Thoracic Surgery*. Boston: Blackwell Scientific Publications, 1989:381, $27.50.

Although both books are useful, I prefer the Gray and Matloff one. The price of the Bojar book is nice.

33. Edmunds LH Jr, Norwood WI, Low DW. *Atlas of Cardiothoracic Surgery*. Philadelphia: Lea & Febiger, 1990:287, $125.00.

One page of illustrations by Dr. Low are presented in apposition to a page of print.

34. Ebert PA. *Atlas of Congenital Cardiac Surgery*. New York: Churchill Livingstone, 1989:138, $125.00.

A great surgeon, Paul Ebert, and a great illustrator, Leon Schlossberg, combine to produce a beautiful book. The page space could have been better utilized.

35. Hopkins RA. *Cardiac Reconstructions with Allograft Valves*. New York: Springer-Verlag, 1989:194, $125.00.

Although allograft cardiovascular tissues have a number of applications, the focus of this volume is on valved ventricular outflow tract reconstructions. This book, which is beautifully illustrated, is a "how-to" guide for surgeons in using allograft valves and conduits in cardiac reconstructions. It will not be a big seller but it is nicely done.

36. Milnor WR. *Hemodynamics*, Second edition. Baltimore: Williams & Wilkins, 1989:419, $74.95.

This book is concerned with the forces generated by the heart and the resulting motion of blood through the cardiovascular system. This book is "heavy" for most cardiologists because physicists and mathematicians have contributed to it equally with physicians and physiologists.

37. Camilleri J-P, Berry CL, Fiessinger J-N, Bariety J, editors. *Diseases of the Arterial Wall*. London: Springer-Verlag, 1989 (English edition): 693, $370.50.

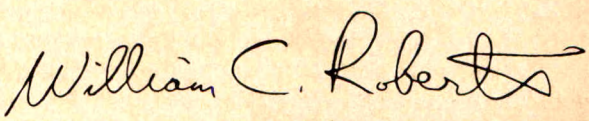
The French edition of this book was published in 1987, and the English translation in 1989. This English edition is a nice heavy book, but it should be. It is the most expensive newly published medical text I have ever seen.

38. Freedom RM. *Pulmonary Atresia with Intact Ventricular Septum*. Mount Kisco, New York: Futura, 1989:262, $55.00.

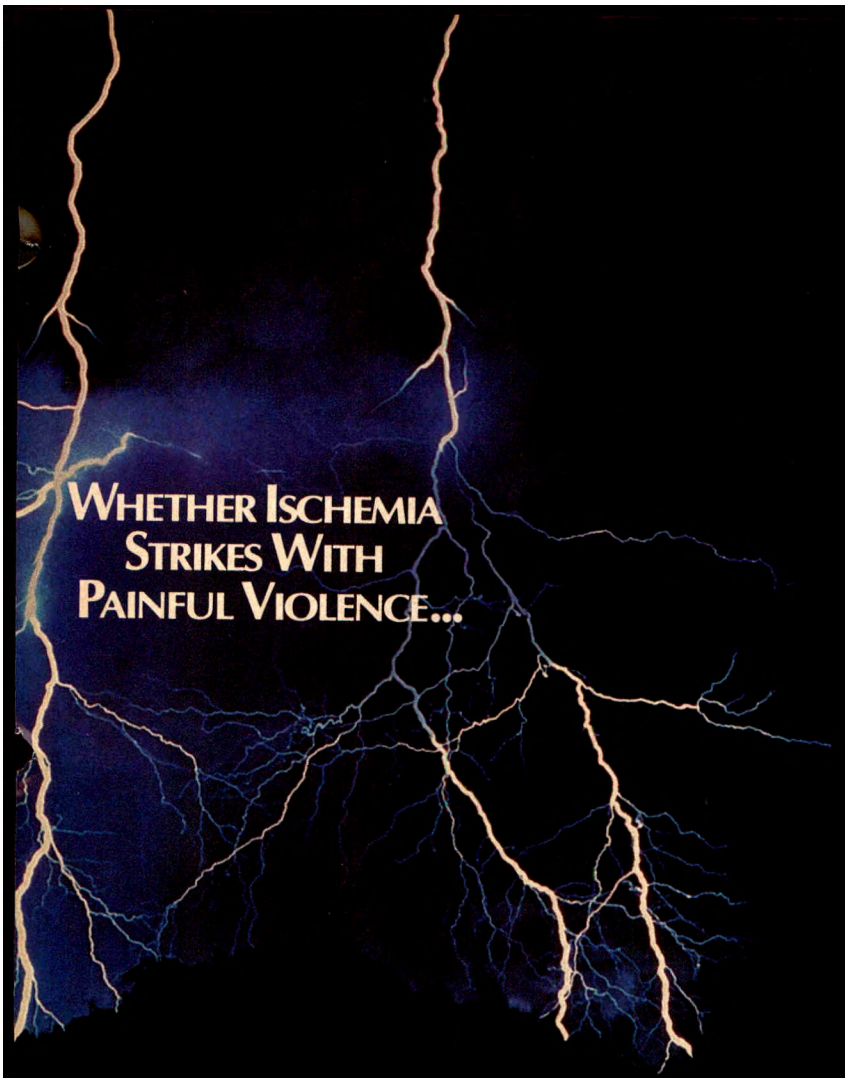
This book includes 19 chapters, 18 of which are written or cowritten by Bob Freedom. One can question whether a defect that makes up <1% of all major congenital cardiac anomalies deserves a separate book, but if information on this defect is desired, here it is.

39. Roberts WC, editor, Mason DT, Rackley CE, Willerson JT, Graham TP Jr, Karp RB. *Cardiology 1989*. Boston: Butterworths, 1989:523, $60.00.

Of course I could be biased but *Cardiology 1989* is really a good book. Articles on the same subject are placed together. A total of 824 articles are summarized and supplemented by 166 figures and 68 tables.



William Clifford Roberts, MD
Editor in Chief



WHETHER ISCHEMIA STRIKES WITH PAINFUL VIOLENCE...

OR TOTAL SILENCE.

TENORMIN reduces more than just *painful* myocardial ischemia. It reduces *painless* ischemia as well. Alone or in combination regimens, it lowers the total ischemic burden* and reduces the need for PRN nitroglycerin.[1-3]

*The sum of painful and painless episodes.

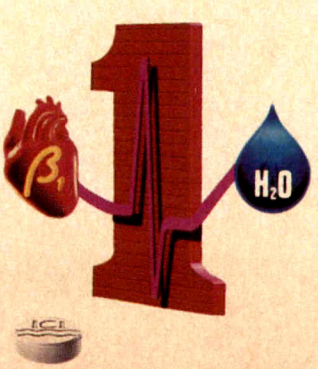
In Angina

ONE TABLET A DAY

TENORMIN®

(atenolol)

PROTECTS THE HEART.



See adjacent page for brief summary of prescribing information.

ONE TABLET A DAY

TENORMIN® (atenolol)



PROTECTS THE HEART FROM PAINFUL AND PAINLESS ISCHEMIA.

A $beta_1$-selective (cardioselective) blocking agent.

DESCRIPTION: TENORMIN (atenolol), a synthetic, $beta_1$-selective (cardioselective) adrenoreceptor blocking agent, may be chemically described as benzeneacetamide, 4-[2′-hydroxy-3′-[(1-methylethyl) amino] propoxy]-. Atenolol (free base) has a molecular weight of 266. It is a relatively polar hydrophilic compound with a water solubility of 26.5 mg/mL at 37°C and a log partition coefficient (octanol/water) of 0.23. It is freely soluble in 1N HCl (300 mg/mL at 25° C) and less soluble in chloroform (3 mg/mL at 25°C).

TENORMIN is available as 50 mg and 100 mg tablets for oral administration.

Inactive ingredients: magnesium stearate, microcrystalline cellulose, povidone, sodium starch glycolate.

INDICATIONS AND USAGE: Hypertension: TENORMIN is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-type diuretic.

Angina Pectoris Due to Coronary Atherosclerosis: TENORMIN is indicated for the long-term management of patients with angina pectoris.

CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure. (See WARNINGS.)

WARNINGS: Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, TENORMIN should be administered cautiously. Both digitalis and atenolol slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic and the response observed closely. If cardiac failure continues despite adequate digitalization and diuresis, TENORMIN should be withdrawn. (See Dosage and Administration.)

Cessation of Therapy With TENORMIN: Patients with coronary artery disease, who are being treated with TENORMIN, should be advised against abrupt discontinuation of therapy. Severe exacerbation of angina and the occurrence of myocardial infarction and ventricular arrhythmias have been reported in angina patients following the abrupt discontinuation of therapy with other beta blockers. The last two complications may occur with or without preceding exacerbation of the angina pectoris. To date, there has been no report of myocardial infarction or severe angina upon withdrawal of TENORMIN, probably due to its long plasma half-life. Because of the problems encountered with other beta blockers, when discontinuation of TENORMIN is planned, the patients should be carefully observed and advised to limit physical activity to a minimum. If the angina worsens or acute coronary insufficiency develops, it is recommended that TENORMIN be promptly reinstituted, at least temporarily. (See Dosage and Administration.)

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative $beta_1$ selectivity, however, TENORMIN may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since $beta_1$ selectivity is not absolute, the lowest possible dose of TENORMIN should be used with therapy initiated at 50 mg, and a $beta_2$-stimulating agent (bronchodilator) should be made available. If dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels.

Anesthesia and Major Surgery: As with all beta-receptor blocking drugs it may be decided to withdraw TENORMIN before surgery. In this case, 48 hours should be allowed to elapse between the last dose and anesthesia. If treatment is continued, care should be taken when using anesthetic agents which depress the myocardium such as ether, cyclopropane, and trichloroethylene.

TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents (eg, dobutamine or isoproterenol with caution—see section on Overdosage). Manifestations of excessive vagal tone (eg, profound bradycardia, hypotension) may be corrected with atropine (1-2 mg IV).

Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm; therefore, patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely. (See Dosage and Administration.)

PRECAUTIONS: Impaired Renal Function: The drug should be used with caution in patients with impaired renal function. (See Dosage and Administration.)

Drug Interactions: Catecholamine-depleting drugs (eg, reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with TENORMIN plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Should it be decided to discontinue therapy in patients receiving beta blockers and clonidine concurrently, the beta blocker should be discontinued several days before the gradual withdrawal of clonidine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human dose, did not indicate a carcinogenic potential in rodents. Results of various mutagenicity studies support this finding.

Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose) was unaffected by atenolol administration.

Animal Toxicology: Chronic studies performed in animals have revealed the occurrence of vacuolation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels of atenolol (starting at 15 mg/kg/day or 7.5 times the maximum recommended human dose), and increased incidence of atrial degeneration of hearts of male rats at 300 mg but not 150 mg atenolol/kg/day (150 and 75 times the maximum recommended human dose, respectively).

USAGE IN PREGNANCY: Pregnancy Category C. Atenolol has been shown to produce a dose-related increase in embryo/fetal resorptions in rats at doses equal to or greater than 50 mg/kg/day or 25 or more times the maximum recommended human dose. Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg/day or 12.5 times the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. TENORMIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Atenolol is excreted in human breast milk at a ratio of 1.5 to 6.8 when compared to the concentration in plasma. Caution should be exercised when TENORMIN is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient. Frequency estimates were derived from controlled studies in which adverse reactions were either volunteered by the patient (US studies) or elicited, eg, by checklist (foreign studies). The reported frequency of elicited adverse effects was higher for both TENORMIN (atenolol) and placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects for TENORMIN and placebo is similar, causal relationship to TENORMIN is uncertain.

The following adverse-reaction data present frequency estimates in terms of percentages: first from the US studies (volunteered side effects) and then from both US and foreign studies (volunteered and elicited side effects):

US STUDIES (% ATENOLOL-% PLACEBO):

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (0%-0.5%), postural hypotension (2%-1%), leg pain (0%-0.5%)

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (4%-1%), vertigo (2%-0.5%), lightheadedness (1%-0%), tiredness (0.6%-0.5%), fatigue (3%-1%), lethargy (1%-0%), drowsiness (0.6%-0%), depression (0.6%-0.5%), dreaming (0%-0%)

GASTROINTESTINAL: diarrhea (2%-0%), nausea (4%-1%)

RESPIRATORY (see WARNINGS): wheeziness (0%-0%), dyspnea (0.6%-1%)

TOTALS US AND FOREIGN STUDIES:

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (12%-5%), postural hypotension (4%-5%), leg pain (3%-1%)

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (13%-6%), vertigo (2%-0.2%), lightheadedness (3%-0.7%), tiredness (26%-13%), fatigue (6%-5%), lethargy (3%-0.7%), drowsiness (2%-0.5%), depression (12%-9%), dreaming (3%-1%)

GASTROINTESTINAL: diarrhea (3%-2%), nausea (3%-1%)

RESPIRATORY (see WARNINGS): wheeziness (3%-3%), dyspnea (6%-4%)

MISCELLANEOUS: There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and, in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy.

POTENTIAL ADVERSE EFFECTS: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects of TENORMIN.

HEMATOLOGIC: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

ALLERGIC: Fever, combined with aching and sore throat, laryngospasm, and respiratory distress.

CENTRAL NERVOUS SYSTEM: Reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation of time and place, short-term memory loss, emotional lability with slightly clouded sensorium, decreased performance on neuropsychometrics.

GASTROINTESTINAL: Mesenteric arterial thrombosis, ischemic colitis.

OTHER: Reversible alopecia, Peyronie's disease, erythematous rash, Raynaud's phenomenon.

MISCELLANEOUS: The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with TENORMIN during investigational use and foreign marketing experience. Furthermore, a number of patients who had previously demonstrated established practolol reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the reaction.

OVERDOSAGE: To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. The most common effects expected with overdosage of a beta-adrenergic blocking agent are bradycardia, congestive heart failure, hypotension, bronchospasm, and hypoglycemia.

In the case of overdosage, treatment with TENORMIN should be stopped and the patient carefully observed. TENORMIN can be removed from the general circulation by hemodialysis. In addition to gastric lavage, the following therapeutic measures are suggested if warranted:

BRADYCARDIA: Atropine or another anticholinergic drug.

HEART BLOCK (SECOND OR THIRD DEGREE): Isoproterenol or transvenous cardiac pacemaker.

CONGESTIVE HEART FAILURE: Conventional therapy.

HYPOTENSION (DEPENDING ON ASSOCIATED FACTORS): Epinephrine rather than isoproterenol or norepinephrine may be useful in addition to atropine and digitalis.

BRONCHOSPASM: Aminophylline, isoproterenol, or atropine.

HYPOGLYCEMIA: Intravenous glucose.

DOSAGE AND ADMINISTRATION: Hypertension: The initial dose of TENORMIN is 50 mg given as one tablet a day either alone or added to diuretic therapy. The full effect of this dose will usually be seen within 1 to 2 weeks. If an optimal response is not achieved, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Increasing the dosage beyond 100 mg a day is unlikely to produce any further benefit.

TENORMIN may be used alone or concomitantly with other antihypertensive agents including thiazide-type diuretics, hydralazine, prazosin, and alpha-methyldopa.

Angina Pectoris: The initial dose of TENORMIN is 50 mg given as one tablet a day. If an optimal response is not achieved within 1 week, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Some patients may require a dosage of 200 mg once a day for optimal effect.

Twenty-four-hour control with once-daily dosing is achieved by giving doses larger than necessary to achieve an immediate maximum effect. The maximum early effect on exercise tolerance occurs with doses of 50 to 100 mg, but at these doses the effect at 24 hours is attenuated, averaging about 50% to 75% of that observed with once-a-day oral doses of 200 mg.

Patients with Renal Impairment: Since TENORMIN is excreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of TENORMIN occurs until creatinine clearance falls below 35 mL/min/1.73 m^2 (normal range is 100-150 mL/min/1.73 m^2); therefore, the following maximum dosages are recommended for patients with renal impairment:

Creatinine Clearance (mL/min/1.73 m^2)	Atenolol Elimination Half-life (h)	Maximum Dosage
15-35	16-27	50 mg daily
<15	>27	50 mg every other day

Patients on hemodialysis should be given 50 mg after each dialysis; this should be done under hospital supervision as marked falls in blood pressure can occur.

Cessation of Therapy: If withdrawal of TENORMIN therapy is planned, it should be achieved gradually over a period of about 2 weeks. Patients should be carefully observed and advised to limit physical activity to a minimum.

HOW SUPPLIED: Tablets of 50 mg atenolol, NDC 0310-0105 (round, flat, uncoated white tablets identified with ICI debossed on one side and 105 debossed on the other side, bisected) are supplied in bottles of 100 tablets and unit-dose packages of 100 tablets.

Tablets of 100 mg atenolol, NDC 0310-0101 (round, flat, uncoated white tablets identified with ICI debossed on one side and 101 debossed on the other side) are supplied in bottles of 100 tablets and unit-dose packages of 100 tablets.

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Journal: Harvey W, Heberden W, Withering W, Stokes W, Murrell W, Einthoven W, Osler W. Anomalies and curiosities of cardiology and of cardiologists. Reflections of famous medical Williams. Am J Cardiol 1984;53:900–915.

Chapter in Book: Cabot RC, White PD, Taussig HB, Levine SA, Wood P, Friedberg CK, Nadas AS, Hurst JW, Braunwald E. How to write cardiologic textbooks. In: Hope JA, ed. A Treatise on Disease of the Heart and Great Vessels. London: Yorke Medical Books, 1984:175–200.

Book: Carrel A, Cutler EC, Gross RE, Blalock A, Craffoord C, Brock RC, Bailey CP, DeBakey ME. The Closing of Holes, Replacing of Valves and Inserting of Pipes, or How Cardiovascular Surgeons Deal with Knives, Knaves and Knots. New York: Yorke University Press, 1984:903.

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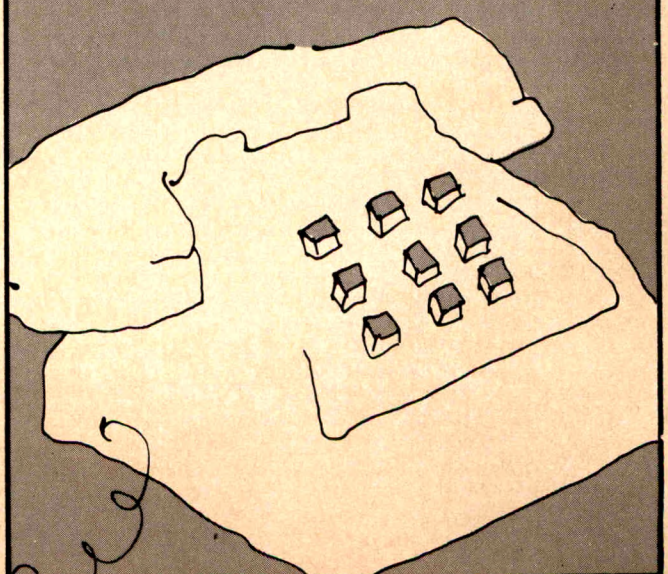
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INDICATIONS AND USAGE
Hypertension
Lopressor tablets are indicated for the treatment of hypertension. They may be used alone or in combination with other antihypertensive agents.

Angina Pectoris
Lopressor is indicated in the long-term treatment of angina pectoris.

Myocardial Infarction
Lopressor ampuls, prefilled syringes, and tablets are indicated in the treatment of hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality. Treatment with intravenous Lopressor can be initiated as soon as the patient's clinical condition allows (see **DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS,** and **WARNINGS**). Alternatively, treatment can begin within 3 to 10 days of the acute event (see **DOSAGE AND ADMINISTRATION**).

CONTRAINDICATIONS
Hypertension and Angina
Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **WARNINGS**).

Myocardial Infarction
Lopressor is contraindicated in patients with a heart rate < 45 beats/min; second- and third-degree heart block; significant first-degree heart block (P-R interval ≥ 0.24 sec); systolic blood pressure < 100 mmHg; or moderate-to-severe cardiac failure (see **WARNINGS**).

WARNINGS
Hypertension and Angina
Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive and angina patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and Lopressor slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic. The response should be observed closely. If cardiac failure continues, despite adequate digitalization and diuretic therapy, Lopressor should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered Lopressor, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1-2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Lopressor administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Lopressor therapy abruptly even in patients treated only for hypertension.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly, and the lowest possible dose of Lopressor should be used. In these circumstances it would be prudent initially to administer Lopressor in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See DOSAGE AND ADMINISTRATION.)**

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial; the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Lopressor, like other beta blockers, is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes and Hypoglycemia: Lopressor should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade, which might precipitate a thyroid storm.

Myocardial Infarction
Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function, and beta blockade carries the potential hazard of depressing myocardial contractility and precipitating or exacerbating minimal cardiac failure.

During treatment with Lopressor, the hemodynamic status of the patient should be carefully monitored. If heart failure occurs or persists despite appropriate treatment, Lopressor should be discontinued.

Bradycardia: Lopressor produces a decrease in sinus heart rate in most patients; this decrease is greatest among patients with high initial heart rates and least among patients with low initial heart rates. Acute myocardial infarction (particularly inferior infarction) may in itself produce significant lowering of the sinus rate. If the sinus rate decreases to < 40 beats/min, particularly if associated with evidence of lowered cardiac output, atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, Lopressor should be discontinued, and cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

AV Block: Lopressor slows AV conduction and may produce significant first- (P-R interval ≥0.26 sec), second-, or third-degree heart block. Acute myocardial infarction also produces heart block.

If heart block occurs, Lopressor should be discontinued and atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

Hypotension: If hypotension (systolic blood pressure ≤ 90 mmHg) occurs, Lopressor should be discontinued, and the hemodynamic status of the patient and the extent of myocardial damage carefully assessed. Invasive monitoring of central venous, pulmonary capillary wedge, and arterial pressures may be required. Appropriate therapy with fluids, positive inotropic agents, balloon counterpulsation, or other treatment modalities should be instituted. If hypotension is associated with sinus bradycardia or AV block, treatment should be directed at reversing these (see above).

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, Lopressor may be used with extreme caution in patients with bronchospastic disease. Because it is unknown to what extent beta$_2$-stimulating agents may exacerbate myocardial ischemia and the extent of infarction, these agents should *not* be used prophylactically. If bronchospasm not related to congestive heart failure occurs, Lopressor should be discontinued. A theophylline derivative or a beta$_2$ agonist may be administered cautiously, depending on the clinical condition of the patient. Both theophylline derivatives and beta$_2$ agonists may produce serious cardiac arrhythmias.**

PRECAUTIONS
General
Lopressor should be used with caution in patients with impaired hepatic function.

Information for Patients
Patients should be advised to take Lopressor regularly and continuously, as directed, with or immediately following meals. If a dose should be missed, the patient should take only the next scheduled dose (without doubling it). Patients should not discontinue Lopressor without consulting the physician.

Patients should be advised (1) to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to therapy with Lopressor has been determined; (2) to contact the physician if any difficulty in breathing occurs; (3) to inform the physician or dentist before any type of surgery that he or she is taking Lopressor.

Laboratory Tests
Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase.

Drug Interactions
Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals have been conducted to evaluate carcinogenic potential. In 2-year studies in rats at three oral dosage levels of up to 800 mg/kg per day, there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in Swiss albino mice at three oral dosage levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor.

All mutagenicity tests performed (a dominant lethal study in mice, chromosome studies in somatic cells, a Salmonella/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) were negative.

No evidence of impaired fertility due to Lopressor was observed in a study performed in rats at doses up to 55.5 times the maximum daily human dose of 450 mg.

Pregnancy Category C
Lopressor has been shown to increase postimplantation loss and decrease neonatal survival in rats at doses up to 55.5 times the maximum daily human dose of 450 mg. Distribution studies in mice confirm exposure of the fetus when Lopressor is administered to the pregnant animal. These studies have revealed no evidence of impaired fertility or teratogenicity. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers
Lopressor is excreted in breast milk in very small quantity. An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug. Caution should be exercised when Lopressor is administered to a nursing woman.

Pediatric Use
Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
Hypertension and Angina
Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression has been reported in about 5 of 100 patients. Mental confusion and short-term memory loss have been reported. Headache, nightmares, and insomnia have also been reported.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations; congestive heart failure; peripheral edema; and hypotension have been reported in about 1 of 100 patients. (See **CONTRAINDICATIONS, WARNINGS,** and **PRECAUTIONS**.)

Respiratory: Wheezing (bronchospasm) and dyspnea have been reported in about 1 of 100 patients (see **WARNINGS**).

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, dry mouth, gastric pain, constipation, flatulence, and heartburn have been reported in about 1 of 100 patients.

Hypersensitive Reactions: Pruritus or rash have occurred in about 5 of 100 patients. Worsening of psoriasis has also been reported.

Miscellaneous: Peyronie's disease has been reported in fewer than 1 of 100,000 patients. Musculoskeletal pain, blurred vision, and tinnitus have also been reported.

There have been rare reports of reversible alopecia, agranulocytosis, and dry eyes. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor.

Myocardial Infarction
Central Nervous System: Tiredness has been reported in about 1 of 100 patients. Vertigo, sleep disturbances, hallucinations, headache, dizziness, visual disturbances, confusion, and reduced libido have also been reported, but a drug relationship is not clear.

Cardiovascular: In the randomized comparison of Lopressor and placebo described in the **CLINICAL PHARMACOLOGY** section, the following adverse reactions were reported:

	Lopressor	*Placebo*
Hypotension (systolic BP < 90 mmHg)	27.4%	23.2%
Bradycardia (heart rate < 40 beats/min)	15.9%	6.7%
Second- or third-degree heart block	4.7%	4.7%
First-degree heart block (P-R ≥ 0.26 sec)	5.3%	1.9%
Heart failure	27.5%	29.6%

Respiratory: Dyspnea of pulmonary origin has been reported in fewer than 1 of 100 patients.

Gastrointestinal: Nausea and abdominal pain have been reported in fewer than 1 of 100 patients.

Dermatologic: Rash and worsened psoriasis have been reported, but a drug relationship is not clear.

Miscellaneous: Unstable diabetes and claudication have been reported, but a drug relationship is not clear.

Potential Adverse Reactions
A variety of adverse reactions not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to Lopressor.

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **CONTRAINDICATIONS**).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Hypersensitive Reactions: Fever combined with aching and sore throat, laryngospasm, and respiratory distress.

OVERDOSAGE
Acute Toxicity
Several cases of overdosage have been reported, some leading to death.

Oral LD_{50}'s (mg/kg): mice, 1158-2460; rats, 3090-4670.

Signs and Symptoms
Potential signs and symptoms associated with overdosage with Lopressor are bradycardia, hypotension, bronchospasm, and cardiac failure.

Treatment
There is no specific antidote.

In general, patients with acute or recent myocardial infarction may be more hemodynamically unstable than other patients and should be treated accordingly (see **WARNINGS, Myocardial Infarction**).

On the basis of the pharmacologic actions of Lopressor, the following general measures should be employed:

Elimination of the Drug: Gastric lavage should be performed.

Bradycardia: Atropine should be administered. If there is no response to vagal blockade, isoproterenol should be administered cautiously.

Hypotension: A vasopressor should be administered, e.g., levarterenol or dopamine.

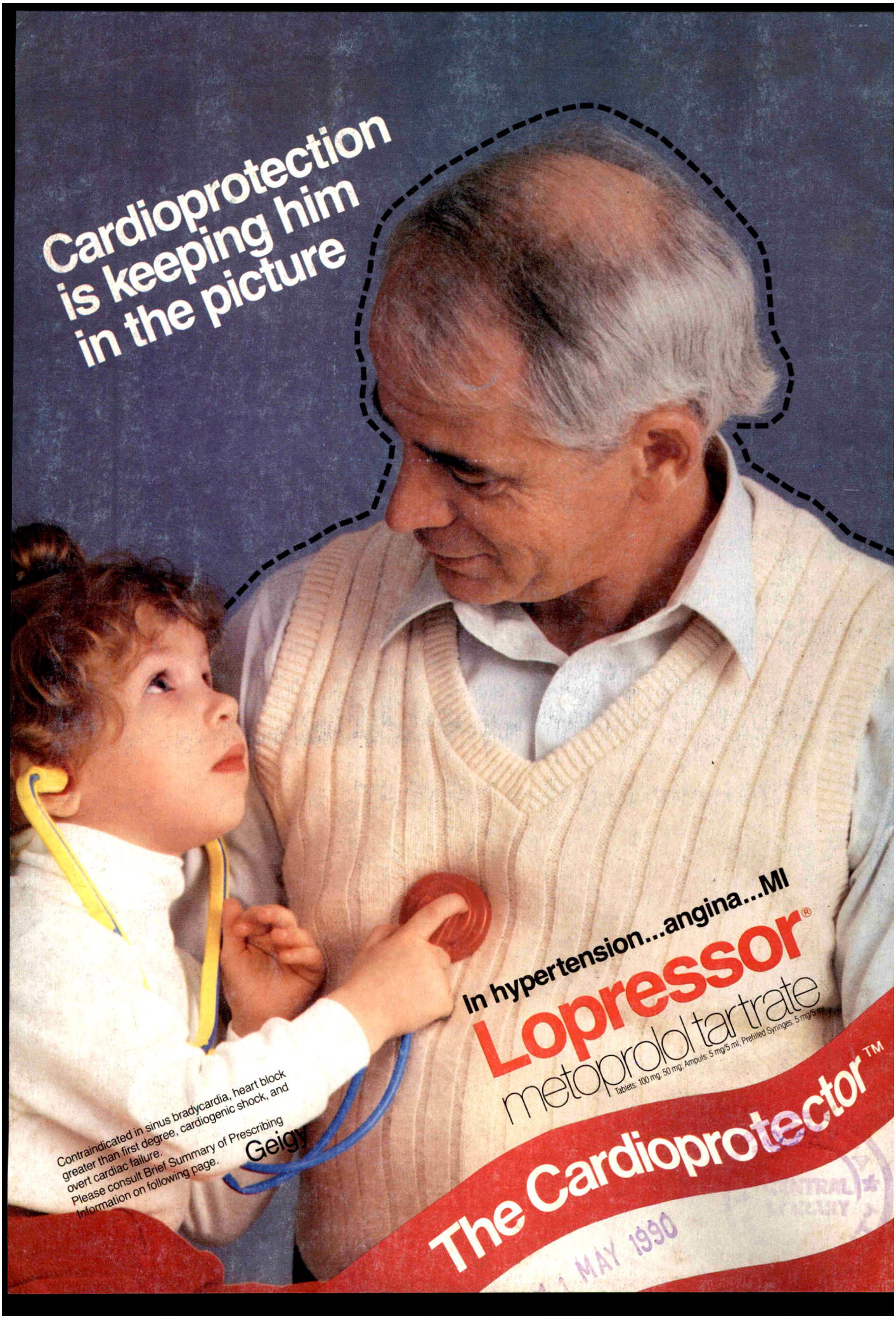
Bronchospasm: A beta$_2$-stimulating agent and/or a theophylline derivative should be administered.

Cardiac Failure: A digitalis glycoside and diuretic should be administered. In shock resulting from inadequate cardiac contractility, administration of dobutamine, isoproterenol, or glucagon may be considered.

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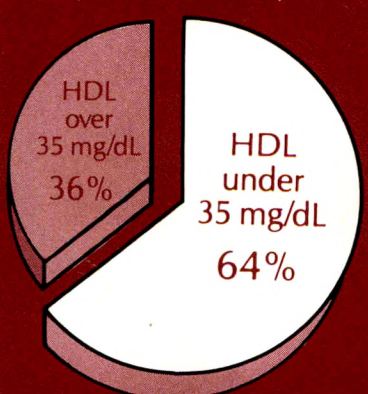
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References: 1. Goldstein JL, Hazzard WR, Schrott HG, Bierman EL, Motulsky AG. Hyperlipidemia in coronary heart disease. I. Lipid levels in 500 survivors of myocardial infarction. *J Clin Invest.* 1973;52:1533-1543. **2.** Assmann G, Schulte H. *PROCAM-Trial: Prospective Cardiovascular Münster Trial.* Zürich: Panscientia Verlag; 1986:8-9. **3.** Data on file, Medical Affairs Dept, Parke-Davis **4.** Tikkanen MJ, Helve E, Jäättelä A, et al. Comparison between lovastatin and gemfibrozil in the treatment of primary hypercholesterolemia: the Finnish Multicenter Study. *Am J Cardiol.* 1988;62:35J-43J.

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Lopid® (Gemfibrozil Capsules and Tablets)

Before prescribing, please see full prescribing information.
A Brief Summary follows.

CONTRAINDICATIONS. 1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.

2. Preexisting gallbladder disease (See WARNINGS).

3. Hypersensitivity to gemfibrozil.

WARNINGS. 1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization (WHO), 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant, 29%, higher total mortality in the clofibrate-treated than in a comparable placebo-treated control group. The excess mortality was due to a 33% increase in noncardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

During the Helsinki Heart Study and in the 1½ year follow-up period since the trial was completed, mortality from any cause was 59 (2.9%) in the Lopid group and 55 (2.7%) in the placebo group. Mortality from any cause during the double-blind portion of the study was 44 deaths in the Lopid group and 43 in the placebo group. Because of the more limited size of the Helsinki Heart Study, this result is not statistically-significantly different from the 29% excess mortality seen in the clofibrate group in the separate WHO study. Noncoronary heart disease related mortality showed a 58% greater trend in the Lopid group (43 vs 27 patients in the placebo group, p=0.056).

In the Helsinki Heart Study, the incidence of total malignancies discovered during the trial and in the 1½ years since the trial was completed was 39 in the Lopid group and 29 in the placebo group (difference not statistically significant). This includes 5 basal cell carcinomas in the Lopid group and none in the placebo group (p=0.06; historical data predicted an expected 4.7 cases in the placebo group). GI malignancies and deaths from malignancies were not statistically different between Lopid and placebo subgroups. Follow-up of the Helsinki Heart Study participants will provide further information on cause-specific mortality and cancer morbidity.

2. A gallstone prevalence substudy of 450 Helsinki Heart Study participants showed a trend toward a greater prevalence of gallstones during the study within the Lopid treatment group (7.5% vs 4.9% for the placebo group, a 55% excess for the gemfibrozil group). A trend toward a greater incidence of gallbladder surgery was observed for the Lopid group (17 vs 11 subjects, a 54% excess). This result did not differ statistically from the increased incidence of cholecystectomy observed in the WHO study in the group treated with clofibrate. Both clofibrate and gemfibrozil may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Lopid therapy should be discontinued if gallstones are found.

3. Since a reduction of mortality from coronary artery disease has not been demonstrated and because liver and interstitial cell testicular tumors were increased in rats, Lopid should be administered only to those patients described in the INDICATIONS AND USAGE section. If a significant serum lipid response is not obtained, Lopid should be discontinued.

4. Concomitant Anticoagulants – Caution should be exercised when anticoagulants are given in conjunction with Lopid. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

5. Concomitant therapy with Lopid and Mevacor® (lovastatin) has been associated with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure (See Drug Interactions). The use of fibrates alone, including Lopid, may occasionally be associated with myositis. Patients receiving Lopid and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myositis, including serum creatine kinase level determination. If myositis is suspected or diagnosed, Lopid therapy should be withdrawn.

6. Cataracts – Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of male rats treated with gemfibrozil at 10 times the human dose.

PRECAUTIONS. 1. **Initial Therapy** – Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal. Before instituting Lopid therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities.

2. **Continued Therapy** – Periodic determination of serum lipids should be obtained, and the drug withdrawn if lipid response is inadequate after 3 months of therapy.

3. **Drug Interactions** – (A) **Lovastatin:** Rhabdomyolysis has occurred with combined gemfibrozil and lovastatin therapy. It may be seen as early as 3 weeks after initiation of combined therapy or after several months. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. There is no assurance that periodic monitoring of creatine kinase will prevent the occurrence of severe myopathy and kidney damage.

(B) **Anticoagulants:** CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

4. **Carcinogenesis, Mutagenesis, Impairment of Fertility** – Long-term studies have been conducted in rats and mice at one and ten times the human dose. The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant (p=0.1). In high dose female rats, there was a significant increase in the combined incidence of benign, and malignant liver neoplasms. In male and female mice, there were no statistically significant differences

Lopid® (Gemfibrozil Capsules and Tablets)

from controls in the incidence of liver tumors, but the doses tested were lower than those shown to be carcinogenic with other fibrates.

Male rats had a dose-related and statistically significant increase of benign Leydig cell tumors at 1 and 10 times the human dose.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following Lopid administration to the male rat. An adequate study to test for peroxisome proliferation has not been done in humans but changes in peroxisome morphology have been observed. Peroxisome proliferation has been shown to occur in humans with either of two other drugs of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Administration of approximately three or ten times the human dose to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to the offspring.

5. **Pregnancy Category B** – Reproduction studies have been performed in the rat at doses 3 and 9 times the human dose, and in the rabbit at 2 and 6.7 times the human dose. These studies have revealed no evidence of impaired fertility in females or harm to the fetus due to Lopid. Minor fetotoxicity was manifested by reduced birth rates observed at the high dose levels. No significant malformations were found among almost 400 offspring from 36 litters of rats and 100 fetuses from 22 litters of rabbits.

There are no studies in pregnant women. In view of the fact that Lopid is tumorigenic in male and female rats, the use of Lopid in pregnancy should be reserved for those patients where the benefit clearly outweighs the possible risk to the patient or fetus.

6. **Nursing Mothers** – Because of the potential for tumorigenicity shown for gemfibrozil in rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

7. **Hematologic Changes** – Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of Lopid therapy. However, these levels stabilize during long-term administration. Rarely, severe anemia, leukopenia, thrombocytopenia, and bone marrow hypoplasia have been reported. Therefore, periodic blood counts are recommended during the first 12 months of Lopid administration.

8. **Liver Function** – Abnormal liver function tests have been observed occasionally during Lopid administration, including elevations of AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase. These are usually reversible when Lopid is discontinued. Therefore periodic liver function studies are recommended and Lopid therapy should be terminated if abnormalities persist.

9. **Use in Children** – Safety and efficacy in children have not been established.

ADVERSE REACTIONS. In the double-blind controlled phase of the Helsinki Heart Study, 2046 patients received Lopid for up to 5 years. In that study, the following adverse reactions were statistically more frequent in subjects in the Lopid group (placebo incidence in parentheses): gastrointestinal reactions, 34.2% (23.8%); dyspepsia, 19.6% (11.9%); abdominal pain, 9.8% (5.6%); acute appendicitis (histologically confirmed in most cases where data are available), 1.2% (0.6%); atrial fibrillation, 0.7% (0.1%).

Adverse events reported by more than 1% of subjects, but without a significant difference between groups (placebo incidence in parentheses) were: diarrhea, 7.2% (6.5%); fatigue, 3.8% (3.5%); nausea/vomiting, 2.5% (2.1%); eczema, 1.9% (1.2%); rash, 1.7% (1.3%); vertigo, 1.5% (1.3%); constipation, 1.4% (1.3%); headache, 1.2% (1.1%).

Gallbladder surgery was performed in 0.9% of Lopid and 0.5% of placebo subjects, a 64% excess, which is not statistically different from the excess of gallbladder surgery observed in the clofibrate compared to the placebo group of the WHO study.

Nervous system and special senses adverse reactions were more common in the Lopid group. These included hypesthesia, paresthesias, and taste perversion. Other adverse reactions that were more common among Lopid treatment group subjects but where a causal relationship was not established include cataracts, peripheral vascular disease, and intracerebral hemorrhage.

From other studies it seems probable that Lopid is causally related to the occurrence of **musculoskeletal symptoms** (See WARNINGS), and to **abnormal liver function tests** and **hematologic changes** (See PRECAUTIONS).

Reports of viral and bacterial infections (common cold, cough, urinary tract infections) were more common in gemfibrozil-treated patients in other controlled clinical trials of 805 patients.

Additional adverse reactions that have been reported for gemfibrozil are listed below by system. These are categorized according to whether a causal relationship to treatment with Lopid is probable or not established:

CAUSAL RELATIONSHIP PROBABLE: *Gastrointestinal:* cholestatic jaundice; *Central Nervous System:* dizziness, somnolence, paresthesia, peripheral neuritis, decreased libido, depression, headache; *Eye:* blurred vision; *Genitourinary:* impotence; *Musculoskeletal:* myopathy, myasthenia, myalgia, painful extremities, arthralgia, synovitis, rhabdomyolysis (see WARNINGS and Drug Interactions under PRECAUTIONS); *Clinical Laboratory:* increased creatine phosphokinase, increased bilirubin, increased liver transaminases (AST [SGOT], ALT [SGPT]), increased alkaline phosphatase; *Hematopoietic:* anemia, leukopenia, bone marrow hypoplasia, eosinophilia; *Immunologic:* angioedema, laryngeal edema, urticaria; *Integumentary:* exfoliative dermatitis, rash, dermatitis, pruritus.

CAUSAL RELATIONSHIP NOT ESTABLISHED: *General:* weight loss; *Cardiac:* extrasystoles; *Gastrointestinal:* pancreatitis, hepatoma, colitis; *Central Nervous System:* confusion, convulsions, syncope; *Eye:* retinal edema; *Genitourinary:* decreased male fertility; *Clinical Laboratory:* positive antinuclear antibody; *Hematopoietic:* thrombocytopenia; *Immunologic:* anaphylaxis, Lupus-like syndrome, vasculitis; *Integumentary:* alopecia.

DOSAGE AND ADMINISTRATION. The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal.

MANAGEMENT OF OVERDOSE. While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

References: 1. Frick MH, Elo O, Haapa K, et al: Helsinki Heart Study: Primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia. *N Engl J Med* 1987;317:1237-1245. 2. Manninen V, Elo O, Frick MH, et al: Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study. *JAMA* 1988; 260:641-651. 3. Nikkila EA: Familial lipoprotein lipase deficiency and related disorders of chylomicron metabolism. In Stanbury J. B. et al. (eds.): *The Metabolic Basis of Inherited Disease,* 5th ed., McGraw-Hill, 1983, Chap. 30, pp. 622-642.

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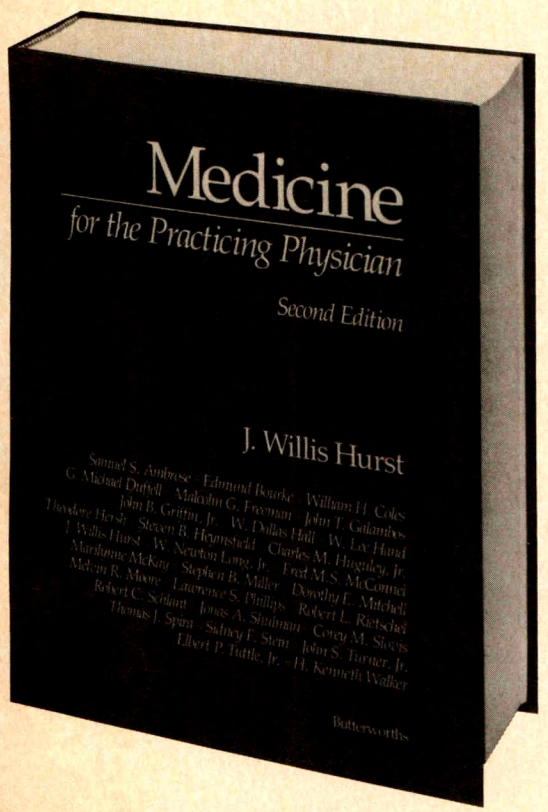
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THE AMERICAN JOURNAL OF CARDIOLOGY.® (ISSN 0002-9149) January 15, 1990, Vol. 65, No. 3 (USPS: 505-750).
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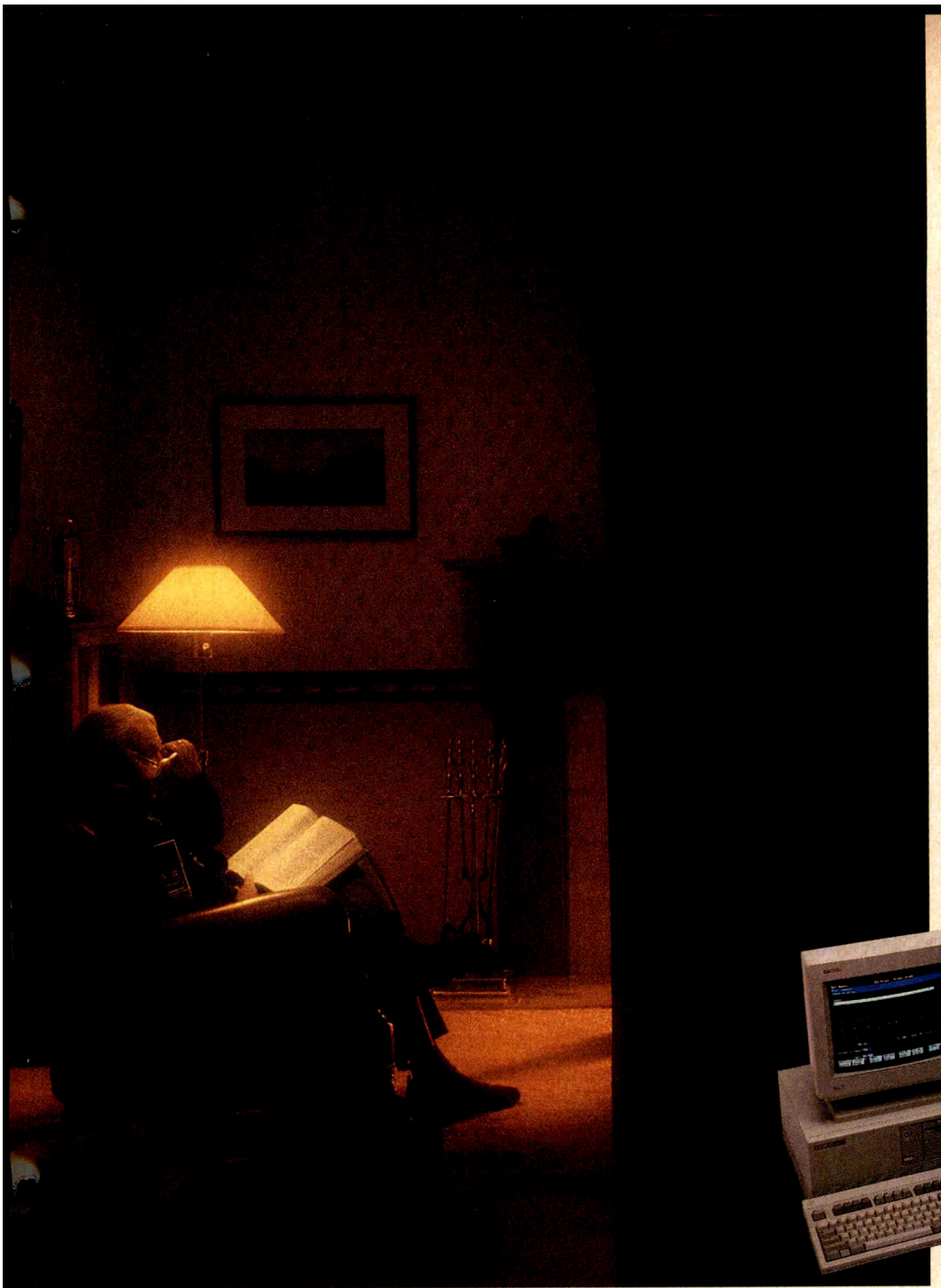
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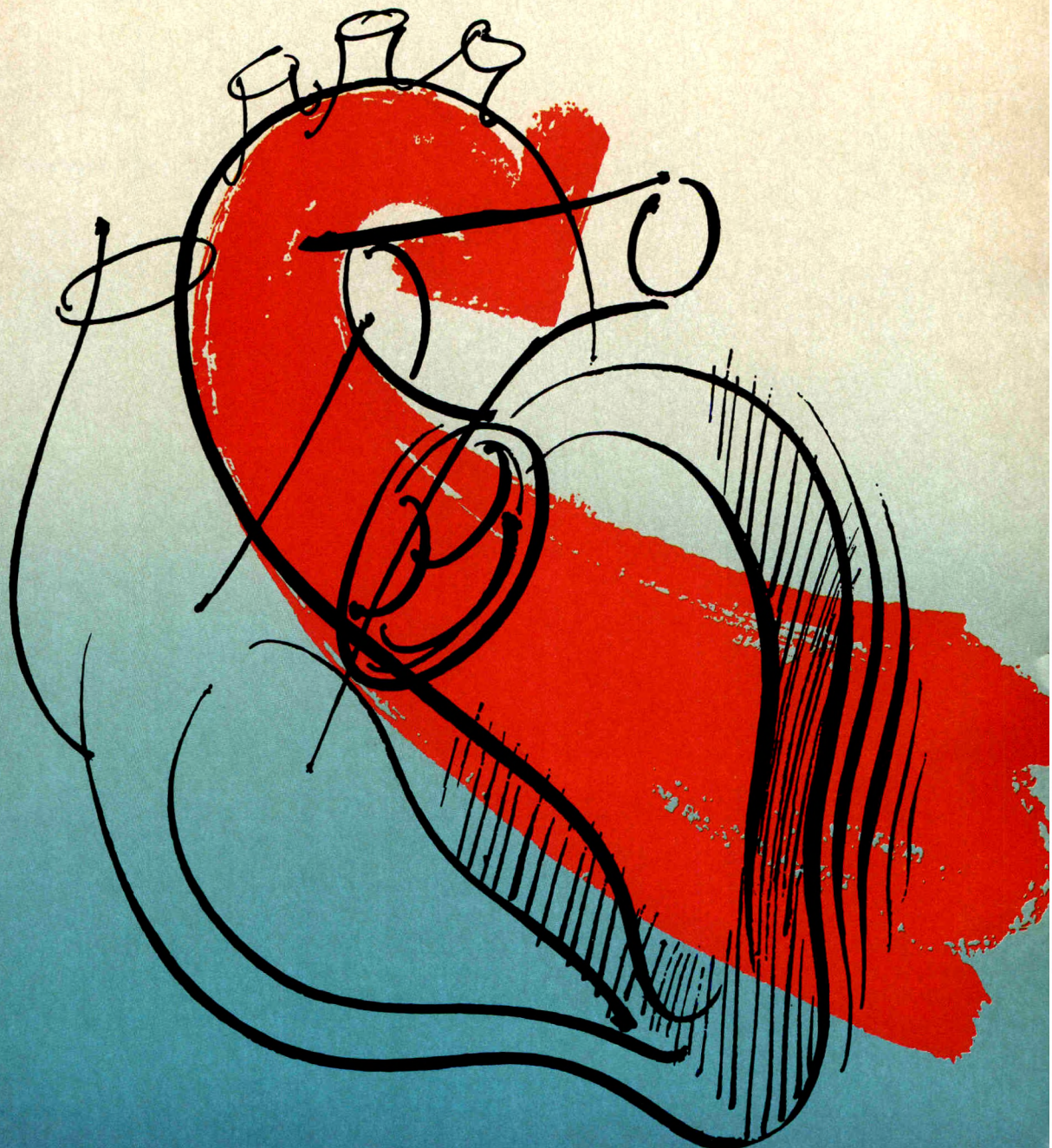
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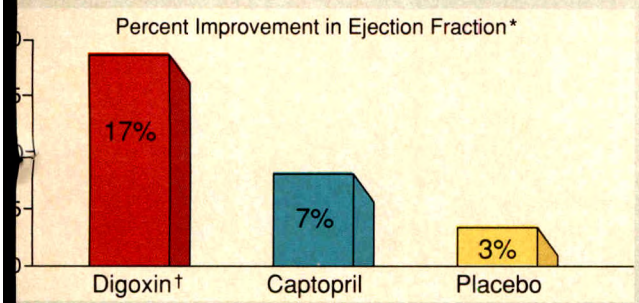
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mproved ejection fraction

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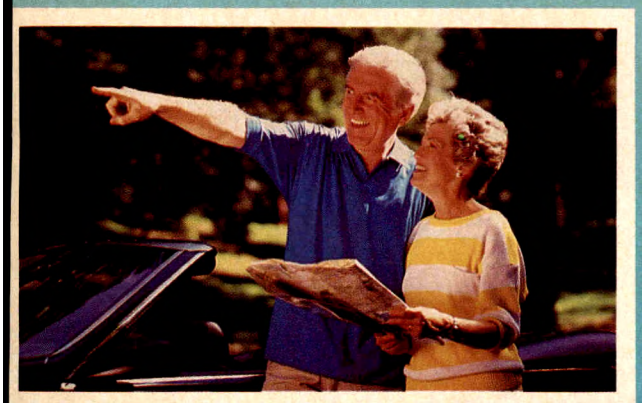
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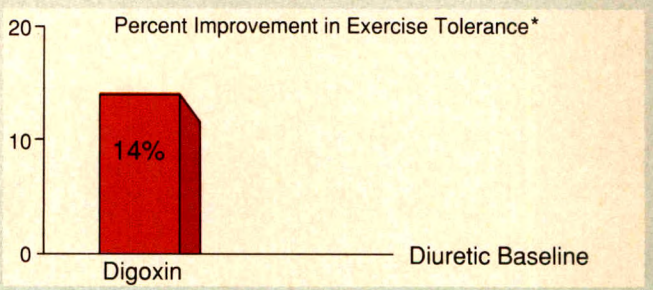
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* Adapted from DiBianco et al.[2]

References: 1. The Captopril-Digoxin Multicenter Research Group: Comparative effects of therapy with captopril and digoxin in patients with mild to moderate heart failure. *JAMA* 1988;259:539-544. **2.** DiBianco R, Shabetai R, Kostuk W, et al: Oral milrinone and digoxin in heart failure: Results of a placebo-controlled, prospective trial of each agent and the combination, abstract. *Circulation* 1987;76(suppl 4):256. **3.** Arnold SB, Byrd RC, Meister W, et al: Long-term digitalis therapy improves left ventricular function in heart failure. *N Engl J Med* 1980;303:1443-1448. **4.** Alicandri C, Fariello R, Boni E, et al: Comparison of captopril and digoxin in mild to moderate heart failure. *Postgrad Med J* 1986;62(suppl 1):170-175.

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INDICATIONS AND USAGE:

Heart Failure: The increased cardiac output resulting from the inotropic action of digoxin ameliorates the disturbances characteristic of heart failure (venous congestion, edema, dyspnea, orthopnea and cardiac asthma).

Digoxin is more effective in "low output" (pump) failure than in "high output" heart failure secondary to arteriovenous fistula, anemia, infection or hyperthyroidism.

Digoxin is usually continued after failure is controlled, unless some known precipitating factor is corrected. Studies have shown, however, that even though hemodynamic effects can be demonstrated in almost all patients, corresponding improvement in the signs and symptoms of heart failure is not necessarily apparent. Therefore, in patients in whom digoxin may be difficult to regulate, or in whom the risk of toxicity may be great (e.g., patients with unstable renal function or whose potassium levels tend to fluctuate) a cautious withdrawal of digoxin may be considered. If digoxin is discontinued, the patient should be regularly monitored for clinical evidence of recurrent heart failure.

CONTRAINDICATIONS: Digitalis glycosides are contraindicated in ventricular fibrillation.

In a given patient, an untoward effect requiring permanent discontinuation of other digitalis preparations usually constitutes a contraindication to digoxin. Hypersensitivity to digoxin itself is a contraindication to its use. Allergy to digoxin, though rare, does occur. It may not extend to all such preparations, and another digitalis glycoside may be tried with caution.

WARNINGS: Digitalis alone or with other drugs has been used in the treatment of obesity. This use of digoxin or other digitalis glycosides is unwarranted. Moreover, since they may cause potentially fatal arrhythmias or other adverse effects, the use of these drugs solely for the treatment of obesity is dangerous.

Anorexia, nausea, vomiting and arrhythmias may accompany heart failure or may be indications of digitalis intoxication. Clinical evaluation of the cause of these symptoms should be attempted before further digitalis administration. In such circumstances determination of the serum digoxin concentration may be an aid in deciding whether or not digitalis toxicity is likely to be present. If the possibility of digitalis intoxication cannot be excluded, cardiac glycosides should be temporarily withheld, if permitted by the clinical situation.

Patients with renal insufficiency require smaller than usual maintenance doses of digoxin (see DOSAGE AND ADMINISTRATION section in the complete prescribing information).

Heart failure accompanying acute glomerulonephritis requires extreme care in digitalization. Relatively low loading and maintenance doses and concomitant use of antihypertensive drugs may be necessary and careful monitoring is essential. Digoxin should be discontinued as soon as possible.

Patients with severe carditis, such as carditis associated with rheumatic fever or viral myocarditis, are especially sensitive to digoxin-induced disturbances of rhythm.

Newborn infants display considerable variability in their tolerance to digoxin. Premature and immature infants are particularly sensitive, and dosage must not only be reduced but must be individualized according to their degree of maturity.

Note: Digitalis glycosides are an important cause of accidental poisoning in children.

PRECAUTIONS:

General: Digoxin toxicity develops more frequently and lasts longer in patients with renal impairment because of the decreased excretion of digoxin. Therefore, it should be anticipated that dosage requirements will be decreased in patients with moderate to severe renal disease (see DOSAGE AND ADMINISTRATION section in the complete prescribing information). Because of the prolonged half-life, a longer period of time is required to achieve an initial or new steady-state concentration in patients with renal impairment than in patients with normal renal function.

In patients with hypokalemia, toxicity may occur despite serum digoxin concentrations within the "normal range", because potassium depletion sensitizes the myocardium to digoxin. Therefore, it is desirable to maintain normal serum potassium levels in patients being treated with digoxin. Hypokalemia may result from diuretic, amphotericin B or corticosteroid therapy, and from dialysis or mechanical suction of gastrointestinal secretions. It may also accompany malnutrition, diarrhea, prolonged vomiting, old age and long-standing heart failure. In general, rapid changes in serum potassium or other electrolytes should be avoided, and intravenous treatment with potassium should be reserved for special circumstances as described below (see TREATMENT OF ARRHYTHMIAS PRODUCED BY OVERDOSAGE section).

Calcium, particularly when administered rapidly by the intravenous route, may produce serious arrhythmias in digitalized patients. Hypercalcemia from any cause predisposes the patient to digitalis toxicity. On the other hand, hypocalcemia can nullify the effects of digoxin in man; thus, digoxin may be ineffective until serum calcium is restored to normal. These interactions are related to the fact that calcium affects contractility and excitability of the heart in a manner similar to digoxin.

Hypomagnesemia may predispose to digitalis toxicity. If low magnesium levels are detected in a patient on digoxin, replacement therapy should be instituted.

Quinidine, verapamil, and amiodarone cause a rise in serum digoxin concentration, with the implication that digitalis intoxication may result. This rise appears to be proportional to the dose. The effect is mediated by a reduction in the digoxin clearance and, in the case of quinidine, decreased volume of distribution as well.

Certain antibiotics may increase digoxin absorption in patients who convert digoxin to inactive metabolites in the gut (see Pharmacokinetics portion of the CLINICAL PHARMACOLOGY section in the complete prescribing information). Recent studies have shown that specific colonic bacteria in the lower gastrointestinal tract convert digoxin to cardioinactive reduction products, thereby reducing its bioavailability. Although inactivation of these bacteria by antibiotics is rapid, the serum digoxin concentration will rise at a rate consistent with the elimination half-life of digoxin. The magnitude of rise in serum digoxin concentration relates to the extent of bacterial inactivation, and may be as much as two-fold in some cases. Patients with acute myocardial infarction or severe pulmonary disease may be unusually sensitive to digoxin-induced disturbances of rhythm.

Atrial arrhythmias associated with hypermetabolic states (e.g. hyperthyroidism) are particularly resistant to digoxin treatment. Large doses of digoxin are not recommended as the only treatment of these arrhythmias and care must be taken to avoid toxicity if large doses of digoxin are required. In hypothyroidism, the digoxin requirements are reduced. Digoxin responses in patients with compensated thyroid disease are normal.

Reduction of digoxin dosage may be desirable prior to electrical cardioversion to avoid induction of ventricular arrhythmias, but the physician must consider the consequences of rapid increase in ventricular response to atrial fibrillation if digoxin is withheld 1 to 2 days prior to cardioversion. If there is a suspicion that digitalis toxicity exists, elective cardioversion should be delayed. If it is not prudent to delay cardioversion, the energy level selected should be minimal at first and carefully increased in an attempt to avoid precipitating ventricular arrhythmias.

Incomplete AV block, especially in patients with Stokes-Adams attacks, may progress to advanced or complete heart block if digoxin is given.

In some patients with sinus node disease (i.e. Sick Sinus Syndrome), digoxin may worsen sinus bradycardia or sinoatrial block.

In patients with Wolff-Parkinson-White Syndrome and atrial fibrillation, digoxin can enhance transmission of impulses through the accessory pathway. This effect may result in extremely rapid ventricular rates and even ventricular fibrillation.

Digoxin may worsen the outflow obstruction in patients with idiopathic hypertrophic subaortic stenosis (IHSS). Unless cardiac failure is severe, it is doubtful whether digoxin should be employed.

Patients with chronic constrictive pericarditis may fail to respond to digoxin. In addition, slowing of the heart rate by digoxin in some patients may further decrease cardiac output.

Patients with heart failure from amyloid heart disease or constrictive cardiomyopathies respond poorly to treatment with digoxin.

Digoxin is not indicated for the treatment of sinus tachycardia unless it is associated with heart failure.

Digoxin may produce false positive ST-T changes in the electrocardiogram during exercise testing.

Intramuscular injection of digoxin is extremely painful and offers no advantages unless other routes of administration are contraindicated.

Laboratory Tests: Patients receiving digoxin should have their serum electrolytes and renal function (BUN and/or serum creatinine) assessed periodically; the frequency of assessments will depend on the clinical setting. For discussion of serum digoxin concentrations, see DOSAGE AND ADMINISTRATION section in the complete prescribing information.

Drug Interactions: Potassium-depleting *corticosteroids* and *diuretics* may be major contributing factors to digitalis toxicity. *Calcium*, particularly if administered rapidly by the intravenous route, may produce serious arrhythmias in digitalized patients. *Quinidine*, *verapamil*, and *amiodarone* cause a rise in serum digoxin concentration, with the implication that digitalis intoxication may result. Certain *antibiotics* increase digoxin absorption in patients who inactivate digoxin by bacterial metabolism in the lower intestine, so that digitalis intoxication may result. *Propantheline* and *diphenoxylate*, by decreasing gut motility, may increase digoxin absorption. *Antacids*, *kaolin-pectin*, *sulfasalazine*, *neomycin*, *cholestyramine* and certain *anticancer drugs* may interfere with intestinal digoxin absorption, resulting in unexpectedly low serum concentrations. There have been inconsistent reports regarding the effects of other drugs on the serum digoxin concentration. *Thyroid* administration to a digitalized hypothyroid patient may increase the dose requirement of digoxin. Concomitant use of digoxin and *sympathomimetics* increases the risk of cardiac arrhythmias because both enhance ectopic pacemaker activity. *Succinylcholine* may cause a sudden extrusion of potassium from muscle cells, and may thereby cause arrhythmias in digitalized patients. Although ß adrenergic blockers or calcium channel blockers and digoxin may be useful in combination to control atrial fibrillation, their additive effects on AV node conduction can result in complete heart block.

Due to the considerable variability of these interactions, digoxin dosage should be carefully individualized when patients receive coadministered medications.

Carcinogenesis, Mutagenesis, Impairment of Fertility: There have been no long-term studies performed in animals to evaluate carcinogenic potential.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C. Animal reproduction studies have not been conducted with digoxin. It is also not known whether digoxin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Digoxin should be given to a pregnant woman only if clearly needed.

Nursing Mothers: Studies have shown that digoxin concentrations in the mother's serum and milk are similar. However, the estimated daily dose to a nursing infant will be far below the usual infant maintenance dose. Therefore, this amount should have no pharmacologic effect upon the infant. Nevertheless, caution should be exercised when digoxin is administered to a nursing woman.

ADVERSE REACTIONS: The frequency and severity of adverse reactions to digoxin depend on the dose and route of administration, as well as on the patient's underlying disease or concomitant therapies (see PRECAUTIONS section). The overall incidence of adverse reactions has been reported as 5 to 20%, with 15 to 20% of them being considered serious (one to four percent of patients receiving digoxin). Evidence suggests that the incidence of toxicity has decreased since the introduction of the serum digoxin assay and improved standardization of digoxin tablets. Cardiac toxicity accounts for about one-half, gastrointestinal disturbances for about one-fourth, and CNS and other toxicity for about one-fourth of these adverse reactions.

Adults:

Cardiac—Unifocal or multiform ventricular premature contractions, especially in bigeminal or trigeminal patterns, are the most common arrhythmias associated with digoxin toxicity in adults with heart disease.

Ventricular tachycardia may result from digitalis toxicity. Atrioventricular (AV) dissociation, accelerated junctional (nodal) rhythm and atrial tachycardia with block are also common arrhythmias caused by digoxin overdosage. Excessive slowing of the pulse is a clinical sign of digoxin overdosage. AV block (Wenckebach) of increasing degree may proceed to complete heart block.

Note: The electrocardiogram is fundamental in determining the presence and nature of these cardiac disturbances. Digoxin may also induce other changes in the ECG (e.g. PR prolongation, ST depression), which represent digoxin effect and may or may not be associated with digitalis toxicity.

Gastrointestinal—Anorexia, nausea, vomiting and less commonly diarrhea are common early symptoms of overdosage. However, uncontrolled heart failure may also produce such symptoms. Digitalis toxicity very rarely may cause abdominal pain and hemorrhagic necrosis of the intestines.

CNS—Visual disturbances (blurred or yellow vision), headache, weakness, apathy and psychosis can occur.

Other—Gynecomastia is occasionally observed.

Infants and Children: Toxicity differs from the adult in a number of respects. Anorexia, nausea, vomiting, diarrhea and CNS disturbances may be present but are rare as initial symptoms in infants. Cardiac arrhythmias are more reliable signs of toxicity. Digoxin in children may produce any arrhythmia. The most commonly encountered are conduction disturbances or supraventricular tachyarrhythmias, such as atrial tachycardia with or without block, and junctional (nodal) tachycardia. Ventricular arrhythmias are less common. Sinus bradycardia may also be a sign of impending digoxin intoxication, especially in infants, even in the absence of first degree heart block. Any arrhythmia or alteration in cardiac conduction that develops in a child taking digoxin should initially be assumed to be a consequence of digoxin intoxication.

TREATMENT OF ARRHYTHMIAS PRODUCED BY OVERDOSAGE:

Adults: Digoxin should be discontinued until all signs of toxicity are gone. Discontinuation may be all that is necessary if toxic manifestations are not severe and appear only near the expected time for maximum effect of the drug.

Potassium salts are commonly used, particularly if hypokalemia is present. Potassium chloride in divided oral doses totaling 3 to 6 grams of the salt (40 to 80 mEq K+) for adults may be given provided renal function is adequate (see below for potassium recommendations in Infants and Children).

When correction of the arrhythmia is urgent and the serum potassium concentration is low or normal, potassium should be administered intravenously in 5% dextrose injection. For adults, a total of 40 to 80 mEq (diluted to a concentration of 40 mEq per 500 ml) may be given at a rate not exceeding 20 mEq per hour, or slower if limited by pain due to local irritation. Additional amounts may be given if the arrhythmia is uncontrolled and potassium well-tolerated. ECG monitoring should be performed to watch for any evidence of potassium toxicity (e.g. peaking of T waves) and to observe the effect on the arrhythmia. The infusion may be stopped when the desired effect is achieved.

Note: Potassium should not be used and may be dangerous in heart block due to digoxin, unless primarily related to supraventricular tachycardia.

Other agents that have been used for the treatment of digoxin intoxication include lidocaine, procainamide, propranolol and phenytoin, although use of the latter must be considered experimental. In advanced heart block, temporary ventricular pacing may be beneficial. Digoxin Immune Fab (Ovine), Digibind®, can be used to reverse potentially life-threatening digoxin (or digitoxin) intoxication. Improvement in signs and symptoms of digitalis toxicity usually begins within ½ hour of Digibind administration. Each 40 mg vial of Digibind will neutralize 0.6 mg of digoxin (which is a usual body store of an adequately digitalized 70 kg patient).

Infants and Children: See Adult section for general recommendations for the treatment of arrhythmias produced by overdosage and for cautions regarding the use of potassium.

If a potassium preparation is used to treat toxicity, it may be given orally in divided doses totaling 1 to 1.5 mEq K+ per kilogram (kg) body weight (1 gram of potassium chloride contains 13.4 mEq K+).

When correction of the arrhythmia with potassium is urgent, approximately 0.5 mEq/kg of potassium per hour may be given intravenously, with careful ECG monitoring. The intravenous solution of potassium should be dilute enough to avoid local irritation; however, especially in infants, care must be taken to avoid intravenous fluid overload.

DOSAGE AND ADMINISTRATION: Recommended dosages are average values that may require considerable modification because of individual sensitivity or associated conditions. Diminished renal function is the most important factor requiring modification of recommended doses.

In deciding the dose of digoxin, several factors must be considered:

1. The disease being treated. Atrial arrhythmias may require larger doses than heart failure.
2. The body weight of the patient. Doses should be calculated based upon lean or ideal body weight.
3. The patient's renal function, preferably evaluated on the basis of creatinine clearance.
4. Age is an important factor in infants and children.
5. Concomitant disease states, drugs or other factors likely to alter the expected clinical response to digoxin (see PRECAUTIONS and Drug Interactions sections).

Consult complete product information before prescribing.

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A Double-Blind Randomized Multicenter Dose-Ranging Trial of Intravenous Streptokinase in Acute Myocardial Infarction

A. Jacob Six, Hans W. Louwerenburg, Reinier Braams, Karel Mechelse, Willem L. Mosterd, Ad C. Bredero, Peter H.J.M. Dunselman, and Norbert M. van Hemel

A double-blind randomized trial was performed to establish the optimal dose of streptokinase. The result of a dosage of 1,500,000 IU is significantly poorer than that of a dosage of 3,000,000 IU ($p < 0.05$); 1,500,000 should not be considered as optimal and is inappropriate for comparison trials with other fibrinolytic agents; further research is needed to establish the efficacy and safety of the 3,000,000 IU dosage.

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Results of High Dose Intravenous Urokinase for Acute Myocardial Infarction

Thomas C. Wall, Harry R. Phillips, III, Richard S. Stack, Susan Mantell, Lynne Aronson, Jane Boswick, Kristina Sigmon, Michael DiMeo, Don Chaplin, David Whitcomb, Depak Pasi, Mark Zawodniak, Moosa Hajisheik, Sadanaud Hegde, Walter Barker, Richard Tenney, and Robert M. Califf

To determine the effectiveness of high dose intravenous urokinase in establishing reperfusion and sustained patency of infarct-related arteries, we prospectively studied 102 patients in the setting of acute myocardial infarction. High dose intravenous urokinase is associated with a 62% patency rate, a low incidence of reocclusion and bleeding complications and a high technical success rate with rescue angioplasty.

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Echocardiographic Evaluation of Segmental Wall Motion Early and Late After Thrombolytic Therapy in Acute Myocardial Infarction: The Western Washington Tissue Plasminogen Activator Emergency Room Trial

Catherine M. Otto, John R. Stratton, Charles Maynard, Ralph Althouse, Karl-Arne Johannessen, and J. Ward Kennedy

In 92 acute myocardial infarction patients treated with tissue plasminogen activator 2.3 ± 1.2 hours after the onset of chest pain, concordance between noninvasive infarct location by electrocardiography or echocardiography and infarct-related artery at angiography 4 ± 2 days later ($n = 85$) was 75.6% and 81.3%, respectively. Improvement in regional wall motion is seen after early treatment with intravenous tissue plasminogen activator.

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Nathan H. Kander, Kurt J. Holland, Bertram Pitt, and Eric J. Topol

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Mitchell W. Krucoff, Nancy B. Wagner, James E. Pope, David M. Mortara, Yvette R. Jackson, Randy K. Bottner, Galen S. Wagner, and Kenneth M. Kent

A newly available electrocardiographic monitor that provides a continuously updated precise digital record of the ST-segment activity of an individual patient has been introduced to produce information that could help triage patients to or away from more aggressive and costly therapy. We describe the salient on-line features of the monitor, various off-line capabilities and examples of its use in 4 specific clinical situations.

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Jens Rokkedal Nielsen, Hans Mickley, Else Marie Damsgaard, and Anders Frøland

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Diwakar Jain, Avijit Lahiri, and Edward B. Raftery, with the technical assistance of Usha Raval

Increased lung thallium-201 uptake was observed in 20 of 62 (32%) patients with acute myocardial infarction who underwent rest thallium-201 imaging within 96 hours of the acute episode. Abnormal lung thallium-201 uptake at rest in AMI is an indicator of the severity of left ventricular dysfunction, and its clinical implications are similar to those of lung thallium-201 uptake seen during exercise in patients with stable coronary artery disease.

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Ability of Dipyridamole–Thallium-201 Imaging One to Four Days After Acute Myocardial Infarction to Predict In-Hospital and Late Recurrent Myocardial Ischemic Events

Kenneth A. Brown, John O'Meara, Charles E. Chambers, and Dennis A. Plante

We tested the ability of dipyridamole–thallium-201 imaging to predict in-hospital and late cardiac events when performed very early (62 ± 21 hours, range 23 to 102) after acute myocardial infarction. Our results suggest that dipyridamole–thallium-201 imaging can identify a subgroup of patients at high risk for early and late ischemic cardiac events who may benefit from early elective invasive diagnostic or therapeutic procedures, as well as patients at very low risk for in-hospital and late ischemic cardiac events.

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Bradford C. Berk, William S. Weintraub, and R. Wayne Alexander

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Mary Ann Lukas Laskey, Ezra Deutsch, John W. Hirshfeld, Jr., William G. Kussmaul, Elliot Barnathan, and Warren K. Laskey

We compared the clinical and angiographic outcome in 2 groups of patients undergoing percutaneous transluminal coronary angioplasty: 18 patients who had not received heparin pretreatment with 35 patients who had. Results show that the addition of prolonged (>24 hours) intravenous heparin administration to the pre-PTCA treatment regimen confers additional benefit to immediate outcome.

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William S. Weintraub, Ellis L. Jones, Spencer B. King III, Joseph Craver, John S. Douglas, Jr., Robert Guyton, Henry Liberman, and Douglas Morris

We studied the use of coronary bypass surgery and percutaneous transluminal coronary angioplasty after diagnostic cardiac catheterization in 14,078 patients. In 1981, 1,704 patients undergoing a first cardiac catheterization had coronary disease, with 51.7% treated medically, 44.0% by bypass grafting and 4.3% with PTCA. In 1988 there were 1,719 patients, with 41.2% treated medically, 28.5% by bypass and 30.3% with PTCA. In the bypass group the percent older than 65 increased from 26.0% in 1981 to 44.9% in 1988. The PTCA population had less severe disease, was younger and had better left ventricular function, and the percent older than 65 increased from 15.4% in 1981 to 35.4% in 1988. The biggest increases in PTCA occurred in 1- and 2-vessel disease, with a decrease in bypass referrals.

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John B. Bedotto, Eric J. Eichhorn, Jeffrey J. Popma, and Gregory J. Dehmer

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K. Atta Boahene, George J. Klein, Arjun D. Sharma, Raymond Yee, and Osamu Fujimura

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Antonis S. Manolis and N.A. Mark Estes, III

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Mark A. Munger, Joseph R. Benotti, Jeffrey A. Green, Robert C. Jarvis, Andrew R. Nara, Jane E. McCue, Robert A. Pospisil, and Richard J. Kasmer

Thirty-three patients with severe congestive heart failure underwent 24-hour intravenous infusion of fenoldopam mesylate titrated to a cardiac index ≥25% above baseline. Cardiac index and stroke volume index were augmented; systemic vascular resistance, left ventricular filling pressure and mean arterial pressure were decreased. Fenoldopam, however, exhibited an attenuation of hemodynamic effects.

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Michael A. Fifer, Cesar R. Molina, Antonio C. Quiroz, Thomas D. Giles, Howard C. Herrmann, Ivan R. De Scheerder, Denis L. Clement, Spencer Kubo, Robert J. Cody, Jay N. Cohn, and Michael B. Fowler

The effects of anaritide, a synthetic analog of atrial natriuretic peptide, were evaluated in 35 patients with chronic congestive heart failure during a 2-phase study. Our findings show that short-term infusion of anaritide produces improvement in hemodynamics and renal function in patients with heart failure.

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Chandra K. Nair, Syed M. Mohiuddin, Daniel E. Hilleman, Richard Schultz, Robert T. Bailey, Jr., Cornelia T. Cook, and Michael H. Sketch, Sr.

Of 165 patients who received a St. Jude valve prosthesis over a 10-year period, 147 were treated with warfarin. The 10-year actuarial event-free incidence from thromboembolic and hemorrhagic events was 84 and 95%, respectively. Thus, use of modest doses of warfarin in patients receiving St. Jude prostheses seems to decrease the incidence of hemorrhagic complications without increasing the incidence of thromboembolic events.

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Kazuo Momma, Atsuyoshi Takao, and Toshimitsu Shibata

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In 15 patients with coronary disease or dilated cardiomyopathy, we analyzed changes in Doppler-derived parameters of left ventricular diastolic filling flow, as well as hemodynamic variables, during the lower body positive and negative pressure method. Results suggest that left atrial pressure is an important determinant of LV early diastolic filling in this setting.

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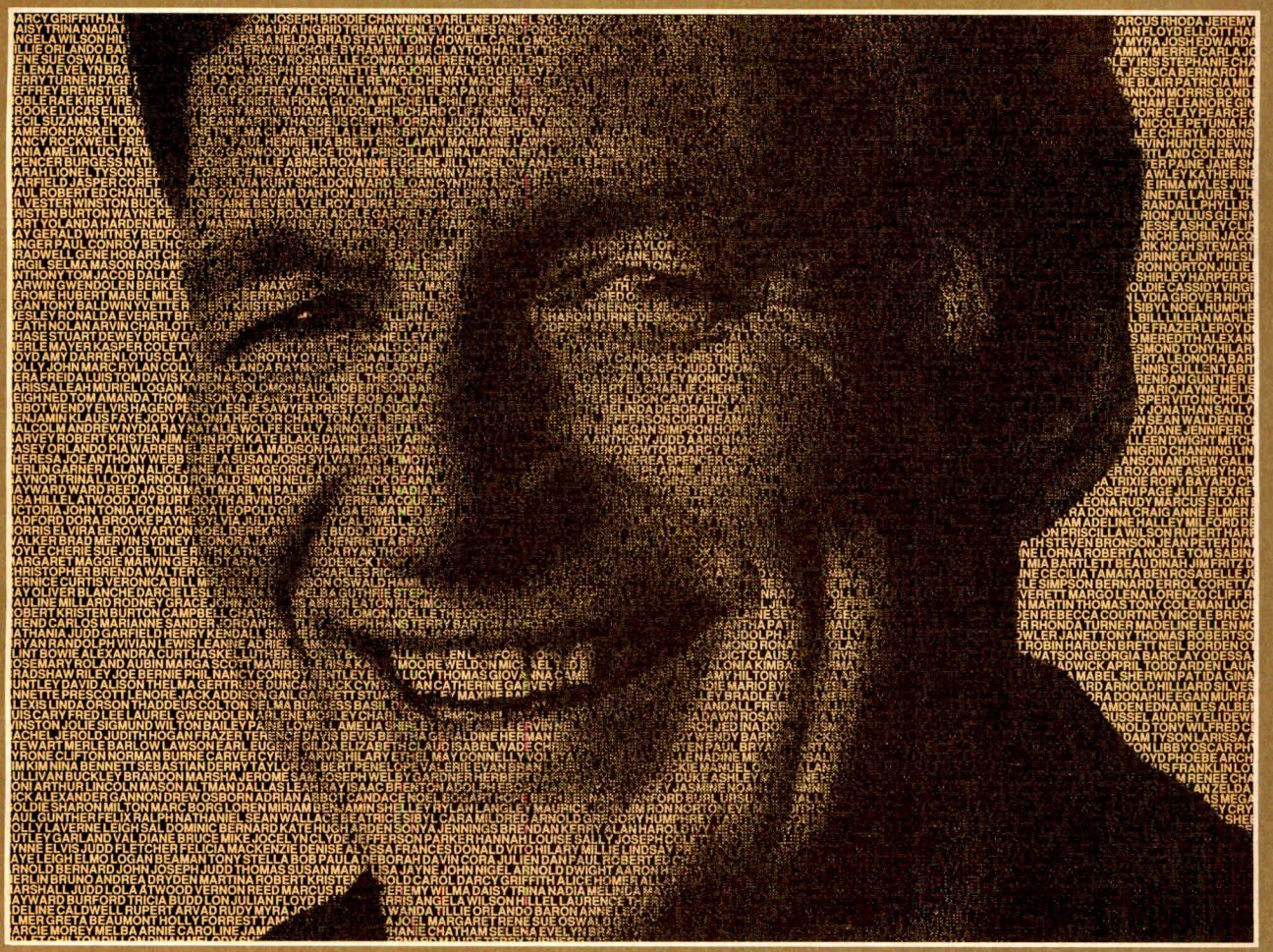
Magnesium Sulfate Is the Treatment for Torsades de Pointes if the Right Dose Is Given

INSTRUCTIONS TO AUTHORS **on page A62**

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MILLION



... like the more than one million patients who have received INDERAL LA for hypertension, angina, and common-migraine prophylaxis.

ONCE-DAILY

INDERAL® LA

(PROPRANOLOL HCl)

LONG ACTING CAPSULES
60, 80, 120, 160 mg

WYETH-AYERST LABORATORIES

THE AMERICAN HEART ASSOCIATION PHARMACEUTICAL ROUNDTABLE

INDERAL LA should not be used in the presence of congestive heart failure, sinus bradycardia, cardiogenic shock, heart block greater than first degree, and bronchial asthma.
Please see adjacent page for brief summary of prescribing information.

BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)*

INDERAL® LA brand of propranolol hydrochloride **(Long Acting Capsules)**

DESCRIPTION. INDERAL LA is formulated to provide a sustained release of propranolol hydrochloride. INDERAL LA is available as 60 mg, 80 mg, 120 mg, and 160 mg capsules.

CLINICAL PHARMACOLOGY. INDERAL is a nonselective, beta-adrenergic receptor-blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor-stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

INDERAL LA Capsules (60, 80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours. When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL Tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially.

INDERAL LA should not be considered a simple mg-for-mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure, and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period.

INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension; it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris.

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary.

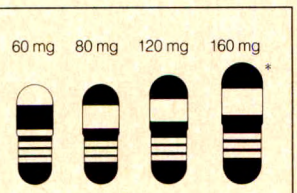
CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock; 2) sinus bradycardia and greater than first-degree block; 3) bronchial asthma; 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

ONCE-DAILY

INDERAL® LA

(PROPRANOLOL HCl)

LONG ACTING CAPSULES



WARNINGS. CARDIAC FAILURE: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned, the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (eg, chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, eg, dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA: Beta blockers should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. Following insulin-induced hypoglycemia, propranolol may cause a delay in the recovery of blood glucose to normal levels.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol may change thyroid function tests, increasing T_4 and reverse T_3, and decreasing T_3.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case, this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS. GENERAL: Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL (propranolol HCl) is not indicated for the treatment of hypertensive emergencies.

Beta-adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

CLINICAL LABORATORY TESTS: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL (propranolol HCl) is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Caution should be exercised when patients receiving a beta blocker are administered a calcium-channel-blocking drug, especially intravenous verapamil, for both agents may depress myocardial contractility or atrioventricular conduction. On rare occasions, the concomitant intravenous use of a beta blocker and verapamil has resulted in serious adverse reactions, especially in patients with severe cardiomyopathy, congestive heart failure, or recent myocardial infarction.

Aluminum hydroxide gel greatly reduces intestinal absorption of propranolol.

Ethanol slows the rate of absorption of propranolol.

Phenytoin, phenobarbitone, and *rifampin* accelerate propranolol clearance.

Chlorpromazine, when used concomitantly with propranolol, results in increased plasma levels of both drugs.

Antipyrine and *lidocaine* have reduced clearance when used concomitantly with propranolol.

Thyroxine may result in a lower than expected T_3 concentration when used concomitantly with propranolol.

Cimetidine decreases the hepatic metabolism of propranolol, delaying elimination and increasing blood levels.

Theophylline clearance is reduced when used concomitantly with propranolol.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

PREGNANCY: Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose.

There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS: INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

PEDIATRIC USE: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: Bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; thrombocytopenic purpura; arterial insufficiency, usually of the Raynaud type.

Central Nervous System: Light-headedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; vivid dreams; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics. For immediate formulations, fatigue, lethargy, and vivid dreams appear dose related.

Gastrointestinal: Nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: Pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: Bronchospasm.

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: Alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from INDERAL Tablets to INDERAL LA Capsules, care should be taken to assure that the desired therapeutic effect is maintained. INDERAL LA should not be considered a simple mg-for-mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels. Retitration may be necessary, especially to maintain effectiveness at the end of the 24-hour dosing interval.

HYPERTENSION — *Dosage must be individualized.* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood-pressure control is achieved. The usual maintenance dosage is 120 to 160 mg once daily. In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

ANGINA PECTORIS — *Dosage must be individualized.* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three- to seven-day intervals until optimal response is obtained. Although individual patients may respond at any dosage level, the average optimal dosage appears to be 160 mg once daily. In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

MIGRAINE — *Dosage must be individualized.* The initial oral dose is 80 mg INDERAL LA once daily. The usual effective dose range is 160-240 mg once daily. The dosage may be increased gradually to achieve optimal migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximal dose, INDERAL LA therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks.

HYPERTROPHIC SUBAORTIC STENOSIS — 80-160 mg INDERAL LA once daily.

PEDIATRIC DOSAGE — At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

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The American Journal of Cardiology

JANUARY 15, 1990, VOL. 65, NO. 3

CORONARY ARTERY DISEASE

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A Double-Blind Randomized Multicenter Dose-Ranging Trial of Intravenous Streptokinase in Acute Myocardial Infarction

A. Jacob Six, Hans W. Louwerenburg, Reinier Braams, Karel Mechelse, Willem L. Mosterd, Ad C. Bredero, Peter H.J.M. Dunselman, and Norbert M. van Hemel

The dosage of 1,500,000 IU streptokinase that is generally applied does not appear to be based on clinical comparative investigations. Therefore, a double-blind randomized trial was carried out to establish the optimal dose. One-hundred eighty-nine patients who had symptoms of acute myocardial infarction for <4 hours were treated with 200,000, 750,000, 1,500,000 or 3,000,000 IU streptokinase intravenously. At coronary angiography 2.8 ± 2.7 hours (mean ± standard deviation) after the start of streptokinase infusion, patency of the infarct-related coronary artery was observed in 38, 75, 60 and 82% of the cases, respectively, in the 4 groups. As the result of a dosage of 1,500,000 IU is significantly poorer than that of a dosage of 3,000,000 IU ($p < 0.05$), the former dosage should not be considered as optimal and is inappropriate for comparison trials with other fibrinolytic agents.

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Results of High Dose Intravenous Urokinase for Acute Myocardial Infarction

Thomas C. Wall, Harry R. Phillips, III, Richard S. Stack, Susan Mantell, Lynne Aronson, Jane Boswick, Kristina Sigmon, Michael DiMeo, Don Chaplin, David Whitcomb, Depak Pasi, Mark Zawodniak, Moosa Hajisheik, Sadanaud Hegde, Walter Barker, Richard Tenney, and Robert M. Califf

To determine the effectiveness of high-dose intravenous urokinase in establishing reperfusion and sustained patency of infarct-related arteries, 102 patients were prospectively studied in the setting of acute myocardial infarction. Sixty-two percent of patients achieved successful thrombolytic reperfusion at the time of immediate catheterization. Although 28% of all patients experienced recurrent ischemia during hospitalization, only 7% experienced reocclusion. Significant bleeding complications were unusual, yet 1 patient experienced an intracranial hemorrhage. Successful rescue angioplasty was achieved in 96% of patients who were occluded at the time

of immediate catheterization. Therefore, high-dose intravenous urokinase is associated with a 62% patency rate, a low incidence of reocclusion and bleeding complications and a high technical success rate with rescue angioplasty.

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Echocardiographic Evaluation of Segmental Wall Motion Early and Late After Thrombolytic Therapy in Acute Myocardial Infarction: The Western Washington Tissue Plasminogen Activator Emergency Room Trial

Catherine M. Otto, John R. Stratton, Charles Maynard, Ralph Althouse, Karl-Arne Johannessen, and J. Ward Kennedy

In 92 acute myocardial infarction patients treated with tissue plasminogen activator 2.3 ± 1.2 hours after the onset of chest pain, concordance between noninvasive infarct location by electrocardiogram or echocardiography and infarct-related artery at angiography 4 ± 2 days later (n = 85) was 75.6% and was 81.3%, respectively. The wall motion score index by echocardiography early after the onset of chest pain (11 ± 14 hours) was worse for anterior (1.8 ± 0.4) versus inferior (1.3 ± 0.2, $p < 0.0001$) or posterior-lateral (1.6 ± 0.2, $p = 0.0003$) infarcts. Overall, the wall motion score index improved from early to late (13 ± 7 weeks) echocardiography (n = 49, 1.5 ± 0.3 to 1.3 ± 0.3, $p = 0.0008$) with improvement confined to those with time to treatment ≤2 hours and evidence of reperfusion at angiography. Echocardiography early after acute myocardial infarction identifies infarct location and regional wall motion improves after early treatment with intravenous tissue plasminogen activator.

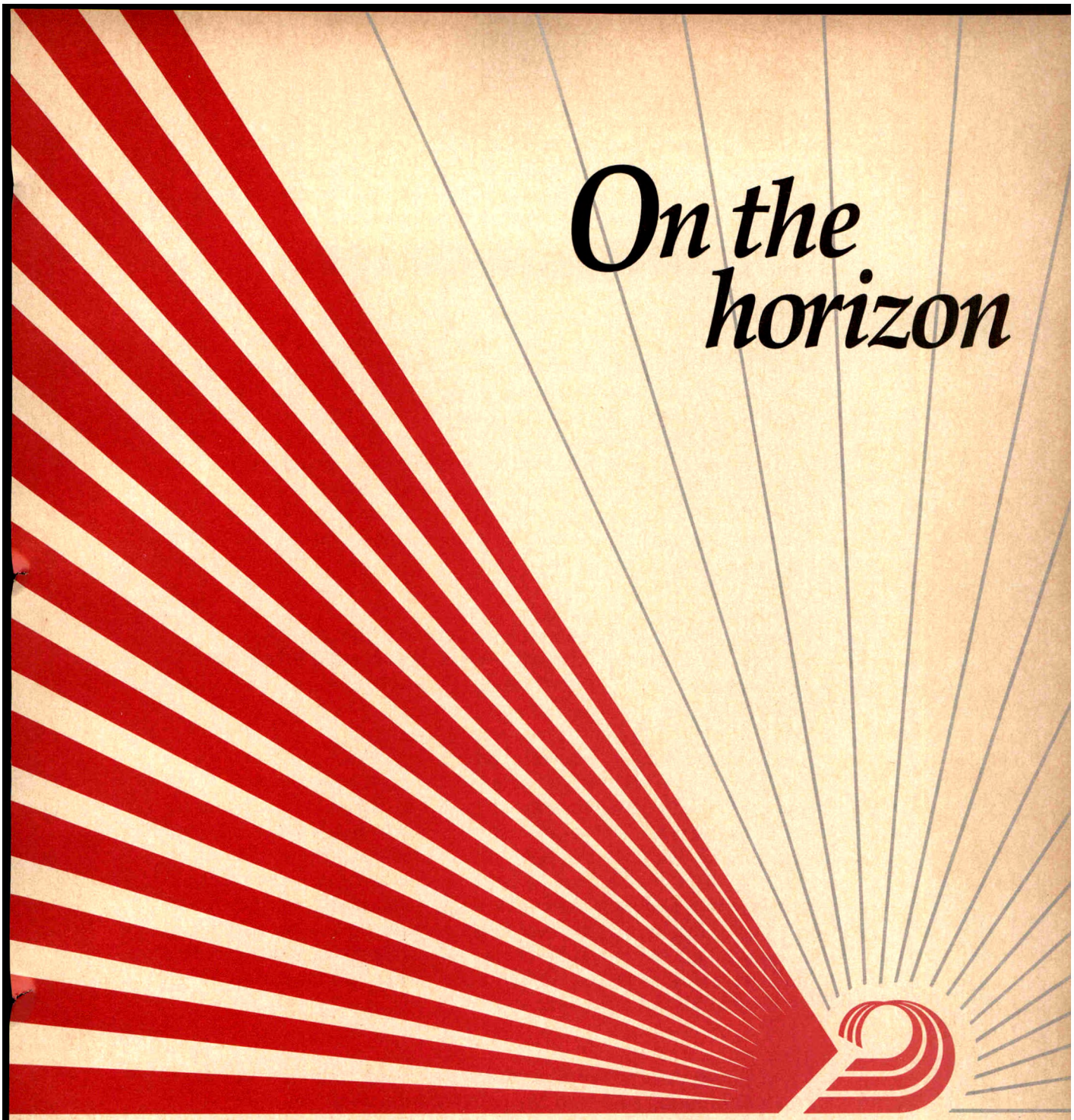
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A Randomized Pilot Trial of Brief Versus Prolonged Heparin After Successful Reperfusion in Acute Myocardial Infarction

Nathan H. Kander, Kurt J. Holland, Bertram Pitt, and Eric J. Topol

To determine the role of heparin, patients with suitable angiographic features after reperfusion therapy were randomly allocated to receive a brief infusion of intravenous heparin for ≤24 hours (group 1), or a prolonged infusion for ≥72 hours (group 2), adjusted to a partial thromboplastin time of 2 times control. Patients were excluded for complex intimal dissections, large residual filling defects, less than Thrombolysis in Myocardial Infarction grade 3 flow pattern or >50% residual stenosis. The primary endpoints were 1-week patency determined by repeat catheterization or recurrent ischemia, or both, and the incidence of bleeding complications. Fifty patients were randomized, 25 in both groups. Baseline variables were similar; 14 group 1 and 15 group 2 patients received thrombolytic treatment; 20 patients in each group had coronary angioplasty. Two documented reocclusions occurred in both groups. Thus, in low-risk patients after successful reperfusion, prolonged heparin therapy does not protect against rethrombosis and is associated with a significantly higher rate of bleeding complications.

Continued on page A18



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The Portable Programmable Microprocessor-Driven Real-Time 12-Lead Electrocardiographic Monitor: A Preliminary Report of a New Device for the Noninvasive Detection of Successful Reperfusion or Silent Coronary Reocclusion

Mitchell W. Krucoff, Nancy B. Wagner, James E. Pope, David M. Mortara, Yvette R. Jackson, Randy K. Bottner, Galen S. Wagner, and Kenneth M. Kent

Despite growing needs, noninvasive indicators of myocardial reperfusion have failed to produce information that could help triage patients to or away from more aggressive and costly therapy. A newly available electrocardiographic monitor that provides a continuously updated precise digital record of the ST-segment activity of an individual patient at bedside has been introduced. The device is especially valuable in monitoring patients during reperfusion therapy to determine the efficacy of such treatment, and in the subsequent hours to signal threatened reocclusion. This report describes the salient on-line features of the monitor, various off-line capabilities and discreet examples of its use in 4 specific clinical situations.

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Predischarge Maximal Exercise Test Identifies Risk for Cardiac Death in Patients with Acute Myocardial Infarction

Jens Rokkedal Nielsen, Hans Mickley, Else Marie Damsgaard, and Anders Frøland

A maximal exercise test was performed in 54 patients with acute myocardial infarction (AMI) before discharge and in 49 age-matched control subjects. The long-term prognosis was assessed after an average follow-up of 7.6 years in AMI patients and 5.8 years in control subjects. A maximal work capacity half that of control subjects predicted long-term mortality in AMI patients. A low increase in systolic blood pressure also predicted long-term mortality, whereas significant ST-segment shifts did not. Maximal work capacity was the best single exercise variable for identifying patients at high risk of cardiac death. Combining all 3 exercise variables the exercise test identified AMI patients at low risk for cardiac death (predictive value of a negative test: 95%).

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Clinical and Prognostic Significance of Lung Thallium Uptake on Rest Imaging in Acute Myocardial Infarction

Diwakar Jain, Avijit Lahiri, and Edward B. Raftery, with the technical assistance of Usha Raval

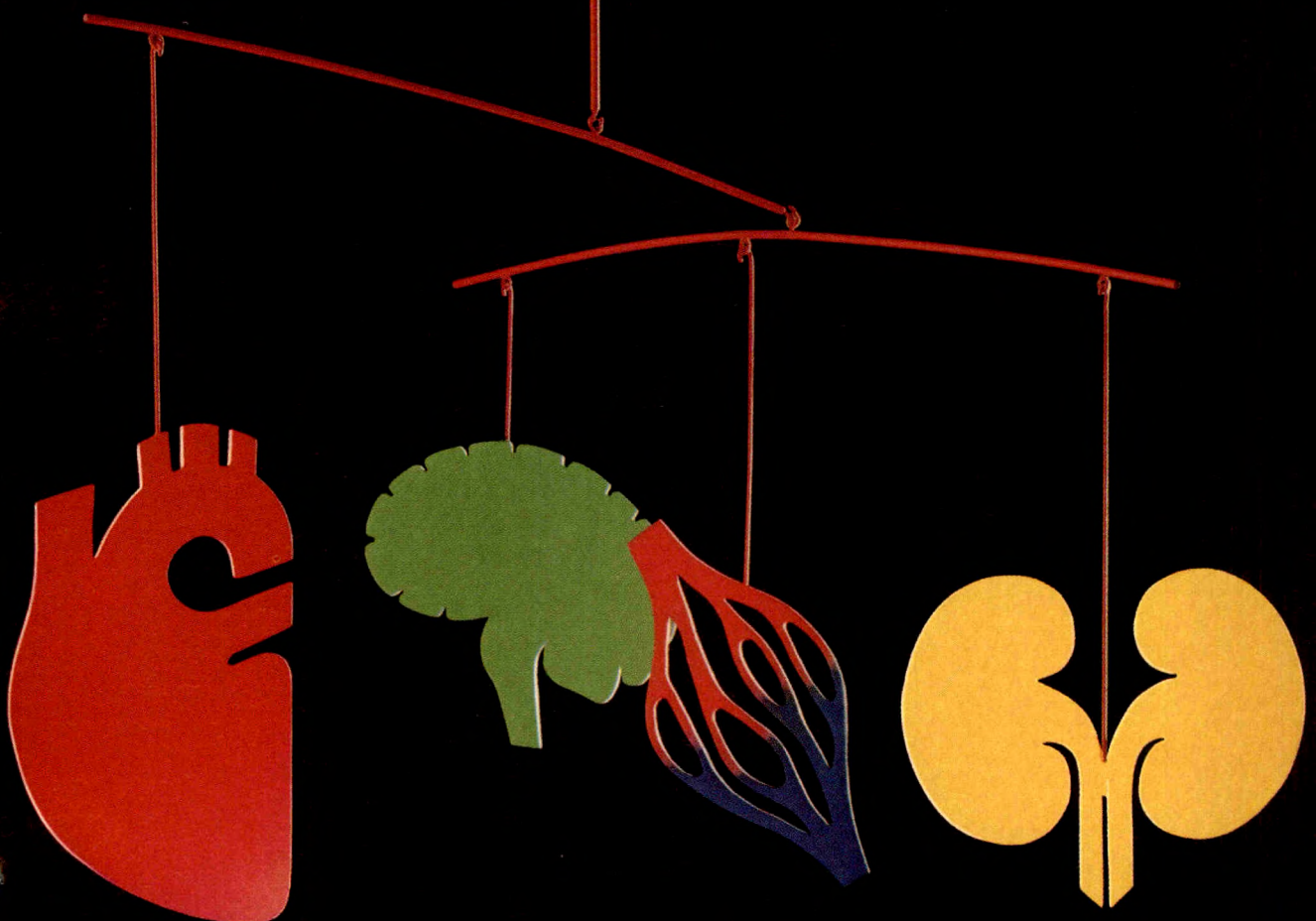
Increased lung thallium-201 uptake was observed in 20 of 62 (32%) patients with acute myocardial infarction (AMI) who underwent rest thallium-201 imaging within 96 hours of the acute episode. The clinical and hemodynamic significance of this observation has been described. Patients with increased lung thallium-201 uptake at rest had significantly higher segmental thallium-201 defect score, wall motion abnormality score, peak CK levels and poorer left ventricular ejection fraction, and had

Continued on page A22

SQUIBB

*In hypertension, in heart failure**

A BALANCE OF BENEFITS FOR YOUR OLDER CV PATIENTS



- Promotes LVH regression[1]
- Tends to sustain cerebral blood flow[2]
- Does not adversely affect lipid profile[3]
- Tends to sustain renal blood flow[4]

Your therapeutic choice today,

CAPOTEN®
(captopril tablets)

can offer patients a lifetime of benefits.

*CAPOTEN is indicated for the treatments of both hypertension and heart failure. CAPOTEN may be used as initial therapy only for hypertensive patients with normal renal function in whom the risk of neutropenia/agranulocytosis is relatively low (1 out of over 8,600 in clinical trials). CAPOTEN also may be used in patients with heart failure who have not responded adequately to treatment with diuretics and digitalis. Although the beneficial effect of captopril in heart failure does not require the presence of digitalis, most controlled clinical trial experience with captopril has been in patients receiving digitalis, as well as diuretic treatment. Consequently, CAPOTEN should generally be added to both of these agents except when digitalis use is poorly tolerated or otherwise not feasible. In using CAPOTEN, consideration should be given to the risk of neutropenia/agranulocytosis. Use special precautions in all patients with impaired renal function, collagen vascular disorders, or those exposed to other drugs known to affect the white blood cells or immune response. Evaluation of hypertensive and heart failure patients should always include assessment of renal function. See INDICATIONS AND USAGE, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS in the brief summary of prescribing information on the adjacent page.

CAPOTEN® (captopril tablets)

Your therapeutic choice today can mean a lifetime of patient benefits

References: 1. 1988 Joint National Committee: The 1988 report of the Joint National Committee on detection, evaluation, and treatment of high blood pressure. Arch Intern Med 148:1023-1038, 1988. **2.** Paulson OB, Waldemar G, Andersen AR, et al: Role of angiotensin in autoregulation of cerebral blood flow. Circulation 77 (suppl I):I-55—I-58, 1988. **3.** Weinberger MH: Antihypertensive therapy and lipids: Evidence, mechanisms, and implications. Arch Intern Med 145:1102-1105, 1985. **4.** Duchin KL, Willard DA: The effect of captopril on renal hemodynamics in hypertensive patients. J Clin Pharmacol 24:351-359, 1984.

CAPOTEN® TABLETS

Captopril Tablets

INDICATIONS: Hypertension—CAPOTEN (captopril) is indicated for the treatment of hypertension. Consideration should be given to the risk of neutropenia/ agranulocytosis (see WARNINGS). CAPOTEN is effective alone and in combination with other antihypertensive agents, especially thiazide-type diuretics.

Heart Failure: CAPOTEN (captopril) is indicated in the treatment of congestive heart failure in patients who have not responded adequately to treatment with diuretics and digitalis. CAPOTEN should generally be added to both of these agents except when digitalis use is poorly tolerated or otherwise not feasible.

CONTRAINDICATIONS: CAPOTEN is contraindicated in patients who are hypersensitive to this product.

WARNINGS: Angioedema—Angioedema involving the extremities, face, lips, mucous membranes, tongue, glottis or larynx has been seen in patients treated with ACE inhibitors, including captopril. If angioedema involves the tongue, glottis or larynx, airway obstruction may occur and be fatal. Emergency therapy, including but not necessarily limited to, subcutaneous administration of a 1:1000 solution of epinephrine should be promptly instituted.

Neutropenia/Agranulocytosis—Neutropenia (<1000/ mm³) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine less than 1.6 mg/dL and no collagen vascular disease), neutropenia has been seen in one patient out of over 8,600 exposed. In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk in clinical trials was about 1 per 500. Doses were relatively high in these patients, particularly in view of their diminished renal function. In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during the subsequent clinical experience. Of reported cases, about half had serum creatinine ≥1.6 mg/dL and more than 75% received procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

Neutropenia has appeared usually within 3 months after starting therapy, associated with myeloid hypoplasia and frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen. Neutrophils generally returned to normal in about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors. **Evaluation of the hypertensive or heart failure patient should always include assessment of renal function.** If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2-week intervals for about 3 months, then periodically. In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever). If infection is suspected, perform white cell counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count <1000/mm³) withdraw captopril and closely follow the patient's course.

Proteinuria: Total urinary proteins >1 g per day were seen in about 0.7% of patients on captopril. About 90% of affected patients had evidence of prior renal disease or received high doses (>150 mg/ day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients. Since most cases of proteinuria occurred by the 8th month of therapy with captopril, patients with prior renal disease or those receiving captopril at doses >150 mg per day, should have urinary protein estimates (dip-stick on 1st morning urine) before therapy, and periodically thereafter.

Hypotension: Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]). In heart failure, where the blood pressure was either normal or low, transient decreases in mean blood pressure >20% were recorded in about half of the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

PRECAUTIONS: General: *Impaired Renal Function*—Hypertension— Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure—About 20% of patients develop stable elevations of BUN and serum creatinine >20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis*—A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis due to decreased afterload reduction. *Surgery/Anesthesia*—If hypotension occurs during surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Drug Interactions: *Hypotension—Patients on Diuretic Therapy*—Precipitous reduction of blood pressure may occasionally occur within the 1st hour after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretics, and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy or by initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least 1 hour after the initial dose.

Agents Having Vasodilator Activity—In heart failure patients, vasodilators should be administered with caution.

Agents Causing Renin Release—Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity—The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium—Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Use potassium-containing salt substitutes with caution.

Inhibitors of Endogenous Prostaglandin Synthesis— Indomethacin and other nonsteroidal anti-inflammatory agents may reduce the antihypertensive effect of captopril, especially in low renin hypertension.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/ kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Pregnancy: Category C: There are no adequate and well-controlled studies in pregnant women. Embryocidal effects and craniofacial malformations were observed in rabbits. Therefore, captopril should be used during pregnancy, or for patients likely to become pregnant, only if the potential benefit outweighs the potential risk to the fetus. Captopril crosses the human placenta.

Nursing Mothers: Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving approximately 7000 patients.

Renal—About 1 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic—Neutropenia/agranulocytosis has occurred (see WARNINGS). Anemia, thrombocytopenia, and pancytopenia have been reported.

Dermatologic—Rash, (usually maculopapular, rarely urticarial), often with pruritus, and sometimes with fever and eosinophilia, in about 4 to 7 of 100 patients (depending on renal status and dose), usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity, have also been reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular—Hypotension may occur; see WARNINGS and PRECAUTIONS [Drug Interactions] for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia—Approximately 2 to 4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months).

Angioedema—Angioedema involving the extremities, face, lips, mucous membranes, tongue, glottis or larynx has been reported in approximately one in 1000 patients. Angioedema involving the upper airways has caused fatal airway obstruction. (See WARNINGS.)

The following have been reported in about 0.5 to 2 percent of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials: gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, cough, alopecia, paresthesias.

Other clinical adverse effects reported since the drug was marketed are listed below by body system. In this setting, an incidence or causal relationship cannot be accurately determined.

General: Asthenia, gynecomastia.
Cardiovascular: Cardiac arrest, cerebrovascular accident, syncope.
Dermatologic: Bullous pemphigus.
Gastrointestinal: Pancreatitis, glossitis.
Hematologic: Anemia, including aplastic and hemolytic.
Hepatobiliary: Hepatitis, including rare cases of necrosis, cholestasis.
Metabolic: Symptomatic hyponatremia.
Musculoskeletal: Myalgia, myasthenia.
Nervous/Psychiatric: Ataxia, confusion, depression, nervousness, somnolence.
Respiratory: Bronchospasm, eosinophilic pneumonitis, rhinitis.
Special Senses: Blurred vision.
Urogenital: Impotence.

As with other ACE inhibitors, a syndrome has been reported which includes: fever, myalgia, arthralgia, rash or other dermatologic manifestations, eosinophilia and an elevated ESR. Findings have usually resolved with discontinuation of treatment.

Altered Laboratory Findings: *Serum Electrolytes: Hyperkalemia:* small increases in serum potassium, especially in patients with renal impairment (see PRECAUTIONS).

Hyponatremia: particularly in patients receiving a low sodium diet or concomitant diuretics.

BUN/Serum Creatinine: Transient elevations of BUN or serum creatinine especially in volume or salt depleted patients or those with renovascular hypertension may occur. Rapid reduction of longstanding or markedly elevated blood pressure can result in decreases in the glomerular filtration rate and, in turn, lead to increases in BUN or serum creatinine.

Hematologic: A positive ANA has been reported.

Liver Function Tests: Elevations of liver transaminases, alkaline phosphatase, and serum bilirubin have occurred.

OVERDOSAGE: Primary concern is correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: CAPOTEN (captopril) should be taken one hour before meals. In hypertension, CAPOTEN may be dosed bid or tid. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function.

Consult package insert before prescribing CAPOTEN (captopril).

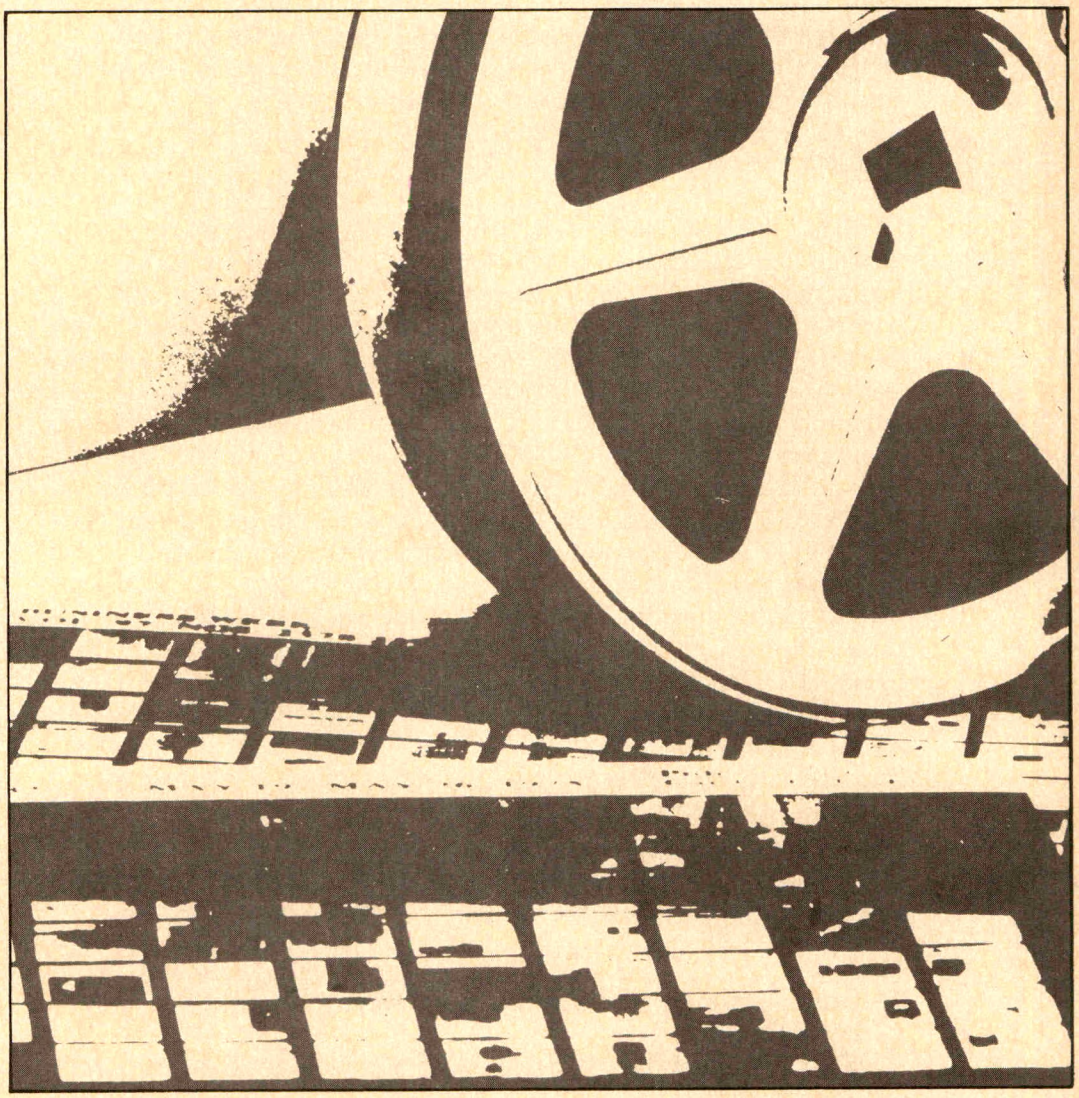
HOW SUPPLIED: Available in tablets of 12.5, 25, and 50 mg in bottles of 100 and 1000; 100 mg in bottles of 100; and in UNIMATIC® unit-dose packs of 100 tablets. (J3-658N)

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higher short-term mortality, compared to those without lung thallium-201 uptake. Of the 34 patients with no evidence of AMI, lung thallium-201 uptake was observed in only 4, of whom 3 had significantly impaired left ventricular function. Abnormal lung thallium-201 uptake at rest in AMI is an indicator of the severity of left ventricular dysfunction and its clinical implications are similar to those of lung thallium-201 uptake seen during exercise in patients with stable coronary artery disease.

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Ability of Dipyridamole–Thallium-201 Imaging One to Four Days After Acute Myocardial Infarction to Predict In-Hospital and Late Recurrent Myocardial Ischemic Events

Kenneth A. Brown, John O'Meara, Charles E. Chambers, and Dennis A. Plante

We tested the ability of dipyridamole–thallium-201 imaging to predict in-hospital and late cardiac events when performed very early (62 ± 21 hours, range 23 to 102) after acute myocardial infarction. In-hospital, 1 patient developed recurrent myocardial infarction and 8 patients developed recurrent angina after infarction associated with ST-segment depression at 60 ± 42 hours after dipyridamole–thallium-201 imaging; of these 6 required urgent revascularization. There were no serious side effects during the dipyridamole–thallium-201 study. Using multivariate logistic regression, the only significant predictor of in-hospital cardiac events was the presence of thallium-201 redistribution within the infarct zone ($p = 0.0001$). Of 20 patients with infarct zone thallium-201 redistribution, 9 (45%) developed in-hospital cardiac events compared to 0 of 30 patients without infarct zone thallium-201 redistribution ($p < 0.0001$). During a follow-up of 12 ± 7 months, 3 additional patients with infarct zone thallium-201 redistribution had recurrent myocardial infarction (2 patients) or unstable angina (1 patient), whereas no patient without infarct zone thallium-201 redistribution had a cardiac event. Dipyridamole–thallium-201 imaging performed very early after an acute myocardial infarction may identify a subgroup of patients at high risk for in-hospital and late cardiac events. Patients without infarct zone thallium-201 redistribution appear to be at very low risk for in-hospital and late ischemic cardiac events and may be candidates for early discharge.

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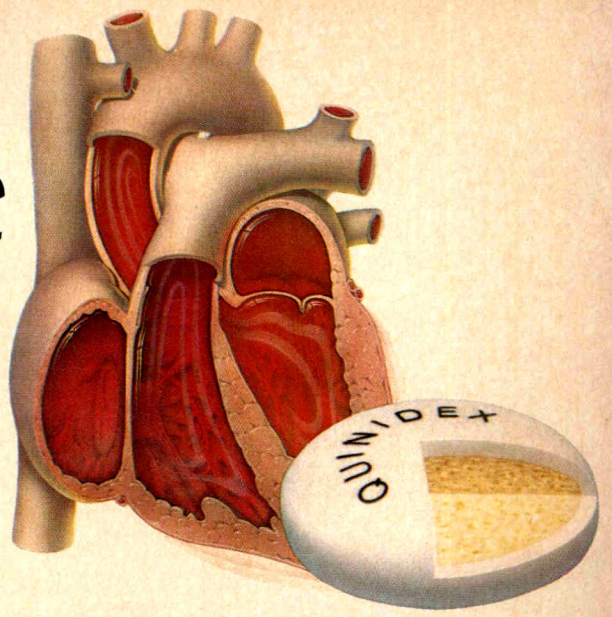
Elevation of C-Reactive Protein in "Active" Coronary Artery Disease

Bradford C. Berk, William S. Weintraub, and R. Wayne Alexander

The role of inflammation in unstable angina was studied by measurement of the acute phase reactant C-reactive protein (CRP) in 3 groups of patients with cardiac disease. Patients admitted to the coronary care unit with a diagnosis of unstable angina had significantly higher ($p = 0.001$) CRP values (2.2 ± 2.9) than coronary care unit patients with nonischemic illnesses (0.9 ± 0.7) or stable angina patients (0.7 ± 0.2). The data suggest that an inflammatory component present in "active" angina may contribute to the abnormal vasoreactivity and thrombosis in these patients.

Continued on page A26

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Please see adjacent page for brief summary.

QUINIDEX
EXTENTABS®
(Quinidine Sulfate Extended-release Tablets, USP) 300 mg

The following is a brief summary only. Before prescribing, see complete prescribing information in Quinidex product labeling.

Contraindications: Intraventricular conduction defects. Complete A-V block. A-V conduction disorders caused by digitalis intoxication. Aberrant impulses and abnormal rhythms due to escape mechanisms. Idiosyncrasy or hypersensitivity to quinidine or related cinchona derivatives. Myasthenia gravis.

Warnings: In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio, resulting in an extremely rapid ventricular rate. This possible hazard may be reduced by digitalization prior to administration of quinidine.

Reports in the literature indicate that serum concentrations of digoxin may increase and may even double when quinidine is administered concurrently. Patients on concomitant therapy should be carefully monitored for digitalis toxicity. Reduction of digoxin dosage may have to be considered.

Manifestations of quinidine cardiotoxicity such as excessive prolongation of the QT interval, widening of the QRS complex and ventricular tachyarrhythmias mandate immediate discontinuation of the drug and/or close clinical and electrocardiographic monitoring.

In susceptible individuals, such as those with marginally compensated cardiovascular disease, quinidine may produce clinically important depression of cardiac function manifested by hypotension, bradycardia, or heartblock. Quinidine therapy should be carefully monitored in such individuals.

Quinidine should be used with extreme caution in patients with incomplete AV block since complete AV block and asystole may be produced. Quinidine may cause abnormalities of cardiac rhythm in digitalized patients and therefore should be used with caution in the presence of digitalis intoxication.

Quinidine should be used with caution in patients exhibiting renal, cardiac or hepatic insufficiency because of potential accumulation of quinidine in serum, leading to toxicity.

Patients taking quinidine occasionally have syncopal episodes which usually result from ventricular tachycardia or fibrillation. This syndrome has not been shown to be related to dose or serum levels. Syncopal episodes frequently terminate spontaneously or in response to treatment, but sometimes are fatal.

Cases of hepatotoxicity, including granulomatous hepatitis, due to quinidine hypersensitivity have been reported. Unexplained fever and/or elevation of hepatic enzymes, particularly in the early stages of therapy, warrant consideration of possible hepatotoxicity. Monitoring liver function during the first 4–8 weeks should be considered. Cessation of quinidine in these cases usually results in the disappearance of toxicity.

Precautions: *General*—All the precautions applying to regular quinidine therapy apply to this product. Hypersensitivity or anaphylactoid reactions to quinidine, although rare, should be considered, especially during the first weeks of therapy. Hospitalization for close clinical observation, electrocardiographic monitoring, and determination of serum quinidine levels are indicated when large doses of quinidine are used or with patients who present an increased risk.

Information for Patients—As with all solid dosage medications, Quinidex Extentabs should be taken with an adequate amount of fluid, preferably with the patient in an upright position to facilitate swallowing. They should be swallowed whole in order to preserve the controlled-release mechanism.

Laboratory Tests—Periodic blood counts and liver and kidney function tests should be performed during long-term therapy; the drug should be discontinued if blood dyscrasias or evidence of hepatic or renal dysfunction occurs.

Drug Interactions

Drug	Effect
Quinidine with anticholinergic drugs	Additive vagolytic effect
Quinidine with cholinergic drugs	Antagonism of cholinergic effects
Quinidine with carbonic anhydrase inhibitors, sodium bicarbonate, thiazide diuretics	Alkalinization of urine resulting in decreased excretion of quinidine
Quinidine with coumarin anticoagulants	Reduction of clotting factor concentrations
Quinidine with tubocurare, succinylcholine and decamethonium	Potentiation of neuromuscular blockade
Quinidine with phenothiazines and reserpine	Additive cardiac depressive effects
Quinidine with hepatic enzyme-inducing drugs (phenobarbital, phenytoin, rifampin)	Decreased plasma half-life of quinidine
Quinidine with digoxin	Increased serum concentration of digoxin (See Warnings)
Quinidine with amiodarone	Increased serum concentration of quinidine
Quinidine with cimetidine	Prolonged quinidine half-life and an increase in serum quinidine level
Quinidine with ranitidine	Premature ventricular contractions and/or bigeminy
Quinidine with verapamil	Increased quinidine half-life and an increase in serum quinidine level; potential hypotensive reactions
Quinidine with nifedipine	Decreased serum concentrations of quinidine

Carcinogenesis: Studies in animals have not been performed to evaluate the carcinogenic potential of quinidine.

Pregnancy, Teratogenic Effects: Pregnancy Category C. Animal reproduction studies have not been conducted with quinidine. There are no adequate and well-controlled studies in pregnant women. Quinidex Extentabs should be administered to a pregnant woman only if clearly indicated.

Nonteratogenic Effects: Like quinine, quinidine has been reported to have oxytocic properties. The significance of this property in the clinical setting has not been established.

Labor and Delivery—There is no known use for Quinidex Extentabs in labor and delivery. However, quinidine has been reported to have oxytocic properties. The significance of this property in the clinical setting has not been established.

Nursing Mothers—Because of passage of the drug into breast milk, caution should be exercised when Quinidex Extentabs are administered to a nursing woman.

Pediatric Use—There are no adequate and well-controlled studies establishing the safety and effectiveness of Quinidex Extentabs in children.

Adverse Reactions: Symptoms of cinchonism, such as ringing in the ears, loss of hearing, dizziness, lightheadedness, headache, nausea, and/or disturbed vision may appear in sensitive patients after a single dose of the drug. The most frequently encountered side effects to quinidine are gastrointestinal.

Gastrointestinal—Nausea, vomiting, abdominal pain, diarrhea, anorexia, granulomatous hepatitis (which may be preceded by fever), esophagitis.

Cardiovascular—Ventricular extrasystoles occurring at a rate of one or more every 6 normal beats; widening of the QRS complex and prolonged QT interval; complete A-V block; ventricular tachycardia and fibrillation; ventricular flutter; torsade de pointes; arterial embolism; hypotension; syncope.

Central Nervous System—Headache, vertigo, apprehension, excitement, confusion, delirium, dementia, ataxia, depression.

Ophthalmologic and Otologic—Disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasis, blurred vision, disturbed color perception, photophobia, diplopia, night blindness, scotomata), optic neuritis, reduced visual field.

Dermatologic—Cutaneous flushing with intense pruritus, photosensitivity, urticaria, rash, eczema, exfoliative eruptions, psoriasis, abnormalities of pigmentation.

Hypersensitivity—Angioedema, acute asthmatic episode, vascular collapse, respiratory arrest, hepatotoxicity, granulomatous hepatitis (See Warnings), purpura, vasculitis.

Hematologic—Thrombocytopenia, thrombocytopenic purpura, agranulocytosis, acute hemolytic anemia, hypoprothrombinemia, leukocytosis, shift to left in WBC differential, neutropenia.

Immunologic—Systemic lupus erythematosus, lupus nephritis.

Miscellaneous—Fever, increase in serum skeletal muscle creatine phosphokinase, arthralgia, myalgia.

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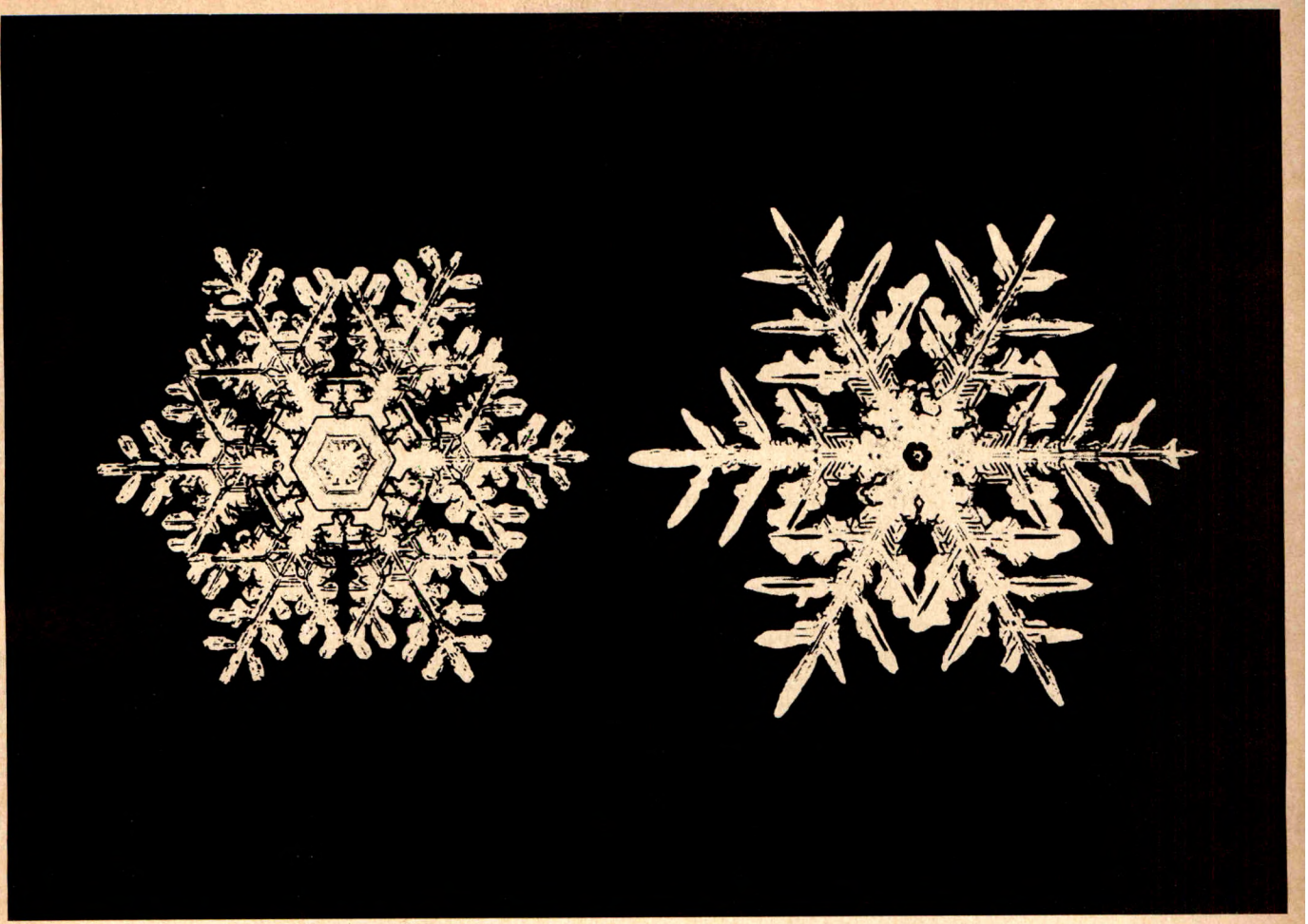
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173
Effects of Glutamate on Exercise Tolerance and Circulating Substrate Levels in Stable Angina Pectoris
Anne Thomassen, Hans E. Bøtker, Torsten T. Nielsen, Kristian Thygesen, and Per Henningsen

To study the effect of glutamate in ischemic heart disease, 20 patients with stable angina pectoris each underwent 4 exercise tests. The first and fourth tests were performed without treatment while the second and third tests were preceded by monosodium glutamate—either 0.8 and 1.5 mg/kg body weight given intravenously (10 patients) or 40 and 80 mg/kg given orally (10 patients). Regardless of route of administration and in a dose-related way, glutamate pretreatment prolonged exercise duration ($p < 0.05$) and delayed the onset of ST-segment depression ($p < 0.05$). Hemodynamics at rest and at comparable workloads were unaffected by glutamate treatment but rate-pressure product at onset of ST-segment depression was increased ($p < 0.05$). This effect was accompanied by 1.5- to 7-fold elevations of plasma glutamate ($p < 0.01$), decreased plasma free fatty acid ($p < 0.001$) and increased plasma alanine concentrations ($p < 0.05$) whereas circulating levels of lactate, glucose, citrate and albumin were not influenced. No adverse effects were seen. Administration of glutamate improves working capacity and ischemic threshold in patients with stable angina pectoris through a metabolic mechanism.

179
Influence of Heparin Therapy on Percutaneous Transluminal Coronary Angioplasty Outcome in Patients with Coronary Arterial Thrombus
Mary Ann Lukas Laskey, Ezra Deutsch, John W. Hirshfeld, Jr., William G. Kussmaul, Elliot Barnathan, and Warren K. Laskey

Acute procedural outcome in 53 patients with intracoronary thrombus was examined with respect to the presence or absence of antecedant systemic heparin therapy. Angiographic success was higher and postprocedural thrombotic vessel occlusion lower in 35 patients receiving preprocedural heparin in comparison to 18 patients not receiving such therapy. This difference existed despite similar clinical and angiographic characteristics.

183
Changing Use of Coronary Angioplasty and Coronary Bypass Surgery in the Treatment of Chronic Coronary Artery Disease
William S. Weintraub, Ellis L. Jones, Spencer B. King III, Joseph Craver, John S. Douglas, Jr., Robert Guyton, Henry Liberman, and Douglas Morris

Use of coronary surgery and percutaneous transluminal coronary angioplasty (PTCA) after diagnostic cardiac catheterization was studied in 14,078 patients. In 1981, 1,704 patients undergoing a first cardiac catheterization had coronary disease, with 51.7% treated medically, 44.0% by coronary artery bypass grafting (CABG) and 4.3% with PTCA. In 1988 there were 1,719 patients, with 41.2% treated medically, 28.5% by CABG

Continued on page A28



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and 30.3% with PTCA. In the CABG group the percent older than 65 increased from 26.0% in 1981 to 44.9% in 1988. The PTCA population had less severe disease, was younger and had better left ventricular function. Nonetheless, the percent older than 65 increased from 15.4% in 1981 to 35.4% in 1988. The biggest increases in PTCA occurred in 1- and 2-vessel disease, with a decrease in the CABG referrals. Thus, 2 processes occurred at the same time. The population grew older and had more significant disease. At the same time PTCA was used with increasing frequency as a treatment for 1- and 2-vessel coronary disease, resulting in a marked shift in the CABG population.

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Effects of Intravenous Isradipine on Left Ventricular Performance During Rapid Atrial Pacing in Coronary Artery Disease

John B. Bedotto, Eric J. Eichhorn, Jeffrey J. Popma, and Gregory J. Dehmer

The effects of intravenous isradipine were evaluated in patients with coronary artery disease using rapid atrial pacing (mean peak heart rate 135 beats/min) to increase myocardial oxygen demand. Intravenous isradipine (0.01 mg/kg, n = 16) or placebo (n = 8) was administered in a double-blind fashion while hemodynamics and left ventricular (LV) function (by digital subtraction angiography) were measured at baseline and during peak pacing. Before isradipine was given, atrial pacing increased diastolic blood pressure and LV end-diastolic pressure measured in the immediate postpacing period while end-diastolic volume index, stroke volume index, ejection fraction and percent regional shortening in 4 of 5 myocardial wall segments decreased. In comparison to the placebo group, isradipine increased baseline heart rate, ejection fraction and stroke volume index and decreased both systolic and diastolic blood pressures and end-systolic volume index before the second pacing period. Compared with the changes during atrial pacing before isradipine, after isradipine systolic and diastolic blood pressures were lower, ejection fraction was higher and percent regional shortening decreased in only 2 of 5 myocardial segments. These results suggest that isradipine has a favorable effect on LV systolic performance both at rest and during rapid atrial pacing in patients with coronary artery disease. Whether these effects are totally explained by the lower blood pressure after isradipine or some other mechanism is not clear, but these findings suggest that isradipine will be useful for the treatment of patients with hypertension or exercise-induced myocardial ischemia.

Continued on page A32

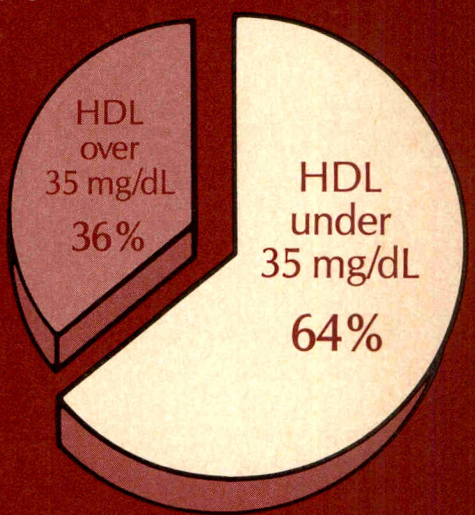
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*Defined as a combination of definite coronary death and/or definite myocardial infarction.

References: 1. Goldstein JL, Hazzard WR, Schrott HG, Bierman EL, Motulsky AG. Hyperlipidemia in coronary heart disease. I. Lipid levels in 500 survivors of myocardial infarction. *J Clin Invest.* 1973;52:1533-1543. **2.** Assmann G, Schulte H. *PROCAM-Trial: Prospective Cardiovascular Münster Trial.* Zürich: Panscientia Verlag; 1986:8-9. **3.** Data on file, Medical Affairs Dept, Parke-Davis.

Please see adjacent page of this advertisement for warnings, contraindications, and brief summary of prescribing information.

PARKE-DAVIS

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Lopid® (Gemfibrozil Capsules and Tablets)

Before prescribing, please see full prescribing information.
A Brief Summary follows.

CONTRAINDICATIONS. 1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.

2. Preexisting gallbladder disease (See WARNINGS).

3. Hypersensitivity to gemfibrozil.

WARNINGS. 1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization (WHO), 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant, 29%, higher total mortality in the clofibrate-treated than in a comparable placebo-treated control group. The excess mortality was due to a 33% increase in noncardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

During the Helsinki Heart Study and in the 1½ year follow-up period since the trial was completed, mortality from any cause was 59 (2.9%) in the Lopid group and 55 (2.7%) in the placebo group. Mortality from any cause during the double-blind portion of the study was 44 deaths in the Lopid group and 43 in the placebo group. Because of the more limited size of the Helsinki Heart Study, this result is not statistically-significantly different from the 29% excess mortality seen in the clofibrate group in the separate WHO study. Noncoronary heart disease related mortality showed a 58% greater trend in the Lopid group (43 vs 27 patients in the placebo group, p=0.056).

In the Helsinki Heart Study, the incidence of total malignancies discovered during the trial and in the 1½ years since the trial was completed was 39 in the Lopid group and 29 in the placebo group (difference not statistically significant). This includes 5 basal cell carcinomas in the Lopid group and none in the placebo group (p=0.06; historical data predicted an expected 4.7 cases in the placebo group). GI malignancies and deaths from malignancies were not statistically different between Lopid and placebo subgroups. Follow-up of the Helsinki Heart Study participants will provide further information on cause-specific mortality and cancer morbidity.

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2. A gallstone prevalence substudy of 450 Helsinki Heart Study participants showed a trend toward a greater prevalence of gallstones during the study within the Lopid treatment group (7.5% vs 4.9% for the placebo group, a 55% excess for the gemfibrozil group). A trend toward a greater incidence of gallbladder surgery was observed for the Lopid group (17 vs 11 subjects, a 54% excess). This result did not differ statistically from the increased incidence of cholecystectomy observed in the WHO study in the group treated with clofibrate. Both clofibrate and gemfibrozil may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Lopid therapy should be discontinued if gallstones are found.

3. Since a reduction of mortality from coronary artery disease has not been demonstrated and because liver and interstitial cell testicular tumors were increased in rats, Lopid should be administered only to those patients described in the INDICATIONS AND USAGE section. If a significant serum lipid response is not obtained, Lopid should be discontinued.

4. Concomitant Anticoagulants—Caution should be exercised when anticoagulants are given in conjunction with Lopid. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

5. Concomitant therapy with Lopid and Mevacor® (lovastatin) has been associated with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure (See Drug Interactions). The use of fibrates alone, including Lopid, may occasionally be associated with myositis. Patients receiving Lopid and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myositis, including serum creatine kinase level determination. If myositis is suspected or diagnosed, Lopid therapy should be withdrawn.

6. Cataracts—Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of male rats treated with gemfibrozil at 10 times the human dose.

PRECAUTIONS. 1. **Initial Therapy**—Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal. Before instituting Lopid therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities.

2. **Continued Therapy**—Periodic determination of serum lipids should be obtained, and the drug withdrawn if lipid response is inadequate after 3 months of therapy.

3. **Drug Interactions**—(A) **Lovastatin:** Rhabdomyolysis has occurred with combined gemfibrozil and lovastatin therapy. It may be seen as early as 3 weeks after initiation of combined therapy or after several months. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. There is no assurance that periodic monitoring of creatine kinase will prevent the occurrence of severe myopathy and kidney damage.

(B) **Anticoagulants:** CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

4. **Carcinogenesis, Mutagenesis, Impairment of Fertility**—Long-term studies have been conducted in rats and mice at one and ten times the human dose. The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant (p=0.1). In high dose female rats, there was a significant increase in the combined incidence of benign, and malignant liver neoplasms. In male and female mice, there were no statistically significant differences

Lopid® (Gemfibrozil Capsules and Tablets)

from controls in the incidence of liver tumors, but the doses tested were lower than those shown to be carcinogenic with other fibrates.

Male rats had a dose-related and statistically significant increase of benign Leydig cell tumors at 1 and 10 times the human dose.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following Lopid administration to the male rat. An adequate study to test for peroxisome proliferation has not been done in humans but changes in peroxisome morphology have been observed. Peroxisome proliferation has been shown to occur in humans with either of two other drugs of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Administration of approximately three or ten times the human dose to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to the offspring.

5. **Pregnancy Category B**—Reproduction studies have been performed in the rat at doses 3 and 9 times the human dose, and in the rabbit at 2 and 6.7 times the human dose. These studies have revealed no evidence of impaired fertility in females or harm to the fetus due to Lopid. Minor fetotoxicity was manifested by reduced birth rates observed at the high dose levels. No significant malformations were found among almost 400 offspring from 36 litters of rats and 100 fetuses from 22 litters of rabbits.

There are no studies in pregnant women. In view of the fact that Lopid is tumorigenic in male and female rats, the use of Lopid in pregnancy should be reserved for those patients where the benefit clearly outweighs the possible risk to the patient or fetus.

6. **Nursing Mothers**—Because of the potential for tumorigenicity shown for gemfibrozil in rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

7. **Hematologic Changes**—Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of Lopid therapy. However, these levels stabilize during long-term administration. Rarely, severe anemia, leukopenia, thrombocytopenia, and bone marrow hypoplasia have been reported. Therefore, periodic blood counts are recommended during the first 12 months of Lopid administration.

8. **Liver Function**—Abnormal liver function tests have been observed occasionally during Lopid administration, including elevations of AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase. These are usually reversible when Lopid is discontinued. Therefore periodic liver function studies are recommended and Lopid therapy should be terminated if abnormalities persist.

9. **Use in Children**—Safety and efficacy in children have not been established.

ADVERSE REACTIONS. In the double-blind controlled phase of the Helsinki Heart Study, 2046 patients received Lopid for up to 5 years. In that study, the following adverse reactions were statistically more frequent in subjects in the Lopid group (placebo incidence in parentheses): gastrointestinal reactions, 34.2% (23.8%); dyspepsia, 19.6% (11.9%); abdominal pain, 9.8% (5.6%); acute appendicitis (histologically confirmed in most cases where data are available), 1.2% (0.6%); atrial fibrillation, 0.7% (0.1%).

Adverse events reported by more than 1% of subjects, but without a significant difference between groups (placebo incidence in parentheses) were: diarrhea, 7.2% (6.5%); fatigue, 3.8% (3.5%); nausea/vomiting, 2.5% (2.1%); eczema, 1.9% (1.2%); rash, 1.7% (1.3%); vertigo, 1.5% (1.3%); constipation, 1.4% (1.3%); headache, 1.2% (1.1%).

Gallbladder surgery was performed in 0.9% of Lopid and 0.5% of placebo subjects, a 64% excess, which is not statistically different from the excess of gallbladder surgery observed in the clofibrate compared to the placebo group of the WHO study.

Nervous system and special senses adverse reactions were more common in the Lopid group. These included hypesthesia, paresthesias, and taste perversion. Other adverse reactions that were more common among Lopid treatment group subjects but where a causal relationship was not established include cataracts, peripheral vascular disease, and intracerebral hemorrhage.

From other studies it seems probable that Lopid is causally related to the occurrence of **musculoskeletal symptoms** (See WARNINGS), and to **abnormal liver function tests** and **hematologic changes** (See PRECAUTIONS).

Reports of viral and bacterial infections (common cold, cough, urinary tract infections) were more common in gemfibrozil-treated patients in other controlled clinical trials of 805 patients.

Additional adverse reactions that have been reported for gemfibrozil are listed below by system. These are categorized according to whether a causal relationship to treatment with Lopid is probable or not established:

CAUSAL RELATIONSHIP PROBABLE: *Gastrointestinal:* cholestatic jaundice; *Central Nervous System:* dizziness, somnolence, paresthesia, peripheral neuritis, decreased libido, depression, headache; *Eye:* blurred vision; *Genitourinary:* impotence; *Musculoskeletal:* myopathy, myasthenia, myalgia, painful extremities, arthralgia, synovitis, rhabdomyolysis (see WARNINGS and Drug Interactions under PRECAUTIONS); *Clinical Laboratory:* increased creatine phosphokinase, increased bilirubin, increased liver transaminases (AST [SGOT], ALT [SGPT]), increased alkaline phosphatase; *Hematopoietic:* anemia, leukopenia, bone marrow hypoplasia, eosinophilia; *Immunologic:* angioedema, laryngeal edema, urticaria; *Integumentary:* exfoliative dermatitis, rash, dermatitis, pruritus.

CAUSAL RELATIONSHIP NOT ESTABLISHED: *General:* weight loss; *Cardiac:* extrasystoles; *Gastrointestinal:* pancreatitis, hepatoma, colitis; *Central Nervous System:* confusion, convulsions, syncope; *Eye:* retinal edema; *Genitourinary:* decreased male fertility; *Clinical Laboratory:* positive antinuclear antibody; *Hematopoietic:* thrombocytopenia; *Immunologic:* anaphylaxis, Lupus-like syndrome, vasculitis; *Integumentary:* alopecia.

DOSAGE AND ADMINISTRATION. The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal.

MANAGEMENT OF OVERDOSE. While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

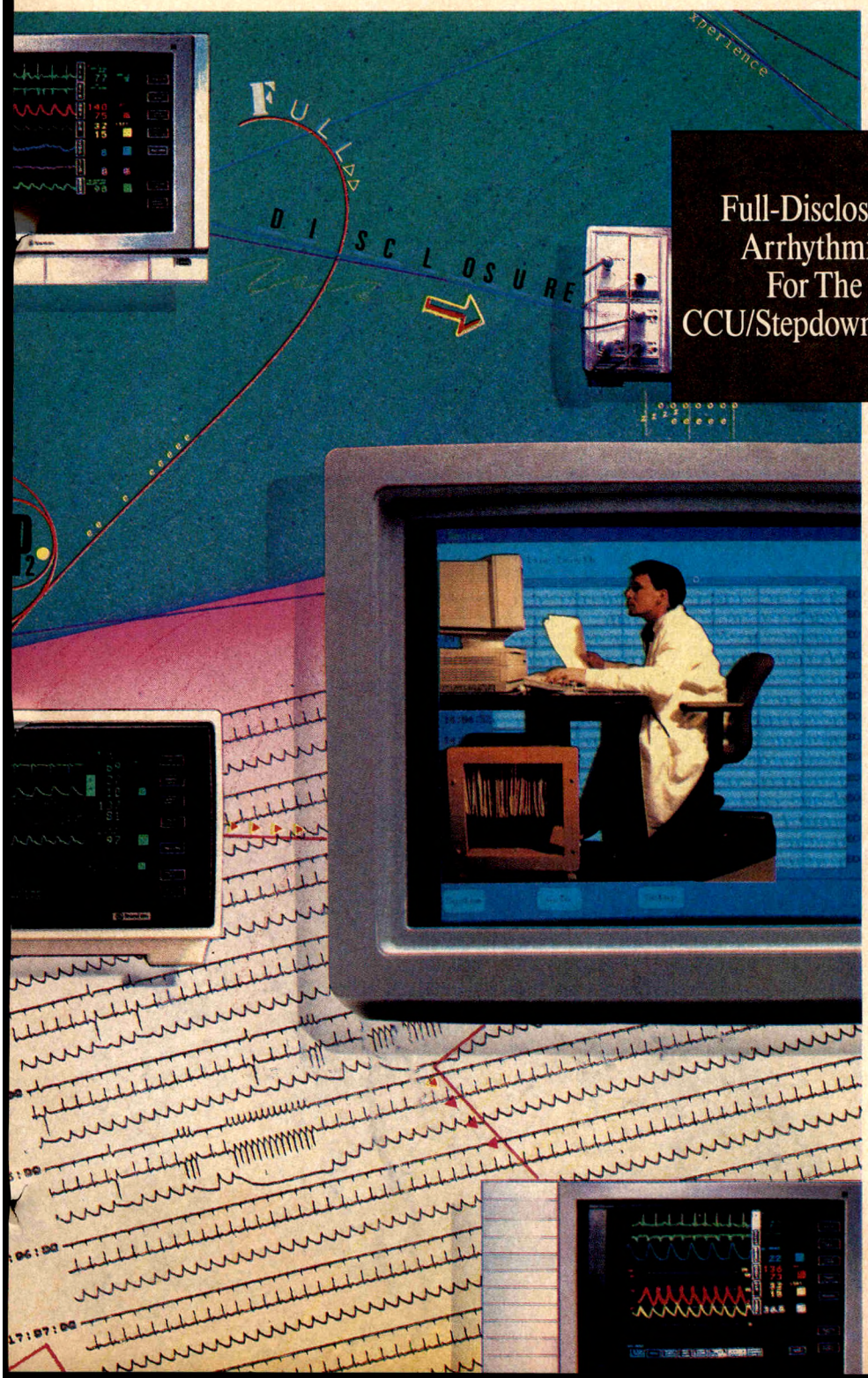
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ARRHYTHMIAS AND CONDUCTION DISTURBANCES

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Value of a Revised Procainamide Test in the Wolff-Parkinson-White Syndrome

K. Atta Boahene, George J. Klein, Arjun D. Sharma, Raymond Yee, and Osamu Fujimura

We evaluated the procainamide test for its ability to predict shortest preexcited RR interval >250 ms during atrial fibrillation in patients with the Wolff-Parkinson-White syndrome. Incremental doses of procainamide (up to a cumulative dose of 1 g) were infused in 33 patients with the Wolff-Parkinson-White syndrome during sinus rhythm. The effect of procainamide on the anterograde effective refractory period of the accessory pathway was dose dependent; patients who lost preexcitation had a steeper dose-response curve. Loss of preexcitation by a cumulative dose of 550 mg provided the optimal balance between sensitivity (60%) and specificity (89%) in identifying patients with preexcited SRR >250 ms. We conclude that the diagnostic accuracy of the procainamide test is critically related to dosage and method of infusion.

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Value of Programmed Ventricular Stimulation in the Evaluation and Management of Patients with Nonsustained Ventricular Tachycardia Associated with Coronary Artery Disease

Antonis S. Manolis and N.A. Mark Estes, III

Programmed ventricular stimulation with a standard protocol was performed in 52 patients with spontaneous nonsustained ventricular tachycardia (VT) associated with coronary artery disease; there were 44 men and 8 women, aged 66 ± 9 years. The mean left ventricular ejection fraction was 41 ± 14%. Nonsustained VT was asymptomatic in 10 patients (19%), while the arrhythmia was detected during evaluation of palpitations in 5 patients (10%), presyncope in 11 (21%) and syncope in 26 patients (50%). All patients were tested in the drug-free state and were classified as having no inducible VT (31 patients, group I), or an inducible arrhythmia (21 patients, group II). The age, gender, type of heart disease, symptoms and left ventricular ejection fraction were similar in both groups, except for a higher overall incidence of syncope in group I. Group I patients received no therapy, while group II patients received antiarrhythmic therapy guided by electropharmacologic testing. At 21 ± 17 months, there was no sustained VT occurrence in either group. One sudden death occurred in group I; 1 patient died of heart failure and 1 patient died of stroke. In group II patients 6 deaths occurred (4 nonsudden cardiac and 2 noncardiac deaths). We conclude that in patients with clinical nonsustained VT associated with coronary artery disease the incidence of significant arrhythmic events is low in patients without therapy with no inducible arrhythmia, and in those with an inducible arrhythmia with therapy guided by electrophysiologic testing.

Continued on page A34

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BRIEF SUMMARY

Contraindications: Severe LV dysfunction (see *Warnings*), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), hypersensitivity to verapamil.

Warnings: Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction < 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported. Several cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (2nd- and 3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol clearance may occur with combined use. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Concomitant use of lithium and verapamil may result in a lowering of serum lithium levels or increased sensitivity to lithium. Patients receiving both drugs must be monitored carefully. Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporin. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use.

Adverse Reactions: Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (2.5%), headache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4%), bradycardia: HR < 50/min (1.4%), AV block: total 1°,2°,3° (1.2%), 2° and 3° (0.8%), rash (1.2%), flushing (0.6%), elevated liver enzymes. The following reactions, reported in 1.0% or less of patients, occurred under conditions where a causal relationship is uncertain: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme, blurred vision, gynecomastia, increased urination, spotty menstruation, impotence. 2/9/89 • A88-W5282V-1

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CONGESTIVE HEART FAILURE

206
Assessment of Hemodynamic Tolerance from a 24-Hour Intravenous Infusion of Fenoldopam Mesylate in Congestive Heart Failure

Mark A. Munger, Joseph R. Benotti, Jeffrey A. Green, Robert C. Jarvis, Andrew R. Nara, Jane E. McCue, Robert A. Pospisil, and Richard J. Kasmer

The invasive hemodynamic profiles of 33 patients with New York Heart Association functional class III to IV congestive heart failure were examined during a 24-hour intravenous infusion of fenoldopam mesylate. The infusion was titrated to an optimal cardiac index (≥25% above baseline). Fenoldopam mesylate augmented cardiac index and stroke volume index while decreasing systemic vascular resistance, left ventricular filling pressure and mean arterial pressure. Attenuation of the hemodynamic effect was noted. None of the parameters exhibited complete attenuation to baseline values. Fenoldopam mesylate demonstrates relative attenuation of pharmacodynamic effect during a 24-hour intravenous infusion.

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Hemodynamic and Renal Effects of Atrial Natriuretic Peptide in Congestive Heart Failure

Michael A. Fifer, Cesar R. Molina, Antonio C. Quiroz, Thomas D. Giles, Howard C. Herrmann, Ivan R. De Scheerder, Denis L. Clement, Spencer Kubo, Robert J. Cody, Jay N. Cohn, and Michael B. Fowler

The effects of anaritide (human atrial natriuretic peptide 102-126), a synthetic analog of atrial natriuretic peptide, were evaluated in 35 patients with heart failure. In response to 1-hour infusions at rates of 0.03 to 0.3 μg/kg/min, there were decreases in mean systemic arterial, pulmonary arterial and pulmonary artery wedge pressures. Cardiac index increased, and heart rate was unchanged. Urine volume, sodium excretion and fractional excretion of sodium increased, while potassium excretion and creatinine clearance did not change. In response to 2-hour infusions at rates of 0.03 to 0.6 μg/kg/min, mean systemic arterial pressure and plasma norepinephrine concentration decreased, while urine volume, sodium excretion and fractional excretion of sodium increased. We conclude that short-term infusion of anaritide produces improvement in hemodynamics and renal function in patients with heart failure.

VALVULAR HEART DISEASE

217
Ten-Year Results with the St. Jude Medical Prosthesis

Chandra K. Nair, Syed M. Mohiuddin, Daniel E. Hilleman, Richard Schultz, Robert T. Bailey, Jr., Cornelia T. Cook, and Michael H. Sketch, Sr.

Of the 165 patients who underwent valve replacement with St. Jude prostheses at our institution, 147 were treated with warfarin. Prothrombin time 1.3 to 1.8 times control (range 15 to 20 seconds) was maintained in

Continued on page A37

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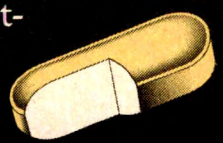
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Brief Summary

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Although most of the studies used dosages exceeding 300 mg, two trials used only 300 mg daily, and pharmacologic data indicate that this dose inhibits platelet function fully. Therefore, 300 mg or a conventional 325 mg aspirin dose daily is a reasonable routine dose that would minimize gastrointestinal adverse reactions. This use of aspirin applies to both solid oral dosage forms (buffered and plain aspirin) and buffered aspirin in solution.

CARDIOVASCULAR AND BIOCHEMICAL:

In the AMIS trial, the dosage of 1,000 mg per day of aspirin was associated with small increases in systolic blood pressure (BP) (average 1.5 to 2.1 mm) and diastolic BP (0.5 to 0.6 mm), depending upon whether maximal or last available readings were used. Blood urea nitrogen and uric acid levels were also increased but by less than 1.0 mg percent. Subjects with marked hypertension or renal insufficiency had been excluded from the trial so that the clinical importance of these observations for such subjects or for any subjects treated over more prolonged periods is not known. It is recommended that patients placed on long-term aspirin treatment, even at doses of 300 mg per day, be seen at regular intervals to assess changes in these measurements.

BIOAVAILABILITY:

The bioavailability of aspirin from Therapy BAYER has been confirmed. In a single-dose study[1] in which plasma acetylsalicylic acid and salicylic acid levels were measured, measurable plasma concentrations were achieved within 15 minutes after dosing. Maximum concentrations were achieved at approximately five hours postdosing. Therapy BAYER, when compared with plain aspirin, achieves maximum plasma salicylate levels not significantly different from plain, i.e., not enteric-coated, aspirin. Dissolution of the enteric coating occurs at a neutral-to-basic pH and is therefore dependent on gastric emptying into the duodenum. With continued dosing, appropriate therapeutic plasma levels are maintained.

SAFETY:

The safety of enteric-coated aspirin has been demonstrated in a number of endoscopic studies comparing enteric-coated aspirin and plain aspirin, as well as plain buffered and "arthritis strength" preparations. In these studies, endoscopies were performed in healthy volunteers before and after either two-day or 14-day administration of aspirin doses of 3,900 or 4,000 mg/day. Compared to all the other preparations, the enteric-coated aspirin produced significantly less damage to the gastric mucosa. There was also statistically less duodenal damage when compared with the plain, i.e., non-enteric-coated, aspirin.

ADVERSE REACTIONS:

Gastrointestinal reactions: Doses of 1,000 mg per day of aspirin caused gastrointestinal symptoms and bleeding that, in some cases, were clinically significant. In the largest postinfarction study (the Aspirin Myocardial Infarction Study [AMIS] with 4,500 people),[2] the percentage of incidences of gastrointestinal symptoms for the aspirin (1,000 mg of a standard, solid-tablet formulation) and placebo-treated subjects, respectively, were stomach pain (14.5%, 4.4%), heartburn (11.9%, 4.8%), nausea and/or vomiting (7.6%, 2.1%), and hospitalization for GI disorder (4.9%, 3.5%). In the AMIS and other trials, aspirin-treated patients had increased rates of gross gastrointestinal bleeding. Symptoms and signs of gastrointestinal irritation were not significantly increased in subjects treated for unstable angina with buffered aspirin in solution.

PROFESSIONAL WARNING:

Occasional reports have documented individuals with impaired gastric emptying in whom there may be retention of one or more enteric-coated aspirin caplets over time. This phenomenon may occur as a result of outlet obstruction from ulcer disease alone or combined with hypotonic gastric peristalsis. Because of the integrity of the enteric coating in an acidic environment, these caplets may accumulate and form a bezoar in the stomach. Individuals with this condition may present with complaints of early satiety or of vague upper abdominal distress. Diagnosis may be made by endoscopy or by abdominal films, which show opacities suggestive of a mass of small caplets.[3] Management may vary according to the condition of the patient. Options include gastrotomy and alternating slightly basic and neutral lavage.[4] While there have been no clinical reports, it has been suggested that such individuals may also be treated with parenteral cimetidine (to reduce acid secretion) and then given sips of slightly basic liquids to effect gradual dissolution of the enteric coating. Progress may be followed with plasma salicylate levels or via recognition of tinnitus by the patient.

It should be kept in mind that individuals with a history of partial or complete gastrectomy may produce reduced amounts of acid and therefore have less acidic gastric pH. Under these circumstances, the benefits offered by the acid-resistant enteric coating may not exist.

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The Bayer Company
90 Park Avenue
New York, NY 10016

134 patients with single and 1.8 to 2 times control (range 20 to 25 seconds) in 13 patients with double valve prostheses. The 10-year actuarial event-free incidence from thromboembolic and hemorrhagic complications was 84 and 95%, respectively. Of the 8 patients receiving antiplatelet therapy alone, 4 had thromboembolic events. Of the 10 patients on neither warfarin nor antiplatelet therapy, 3 had thromboembolic events. The 10-year actuarial event-free incidence from valve failure was 95%. The 10-year actuarial patient survival was 55%.

CARDIOMYOPATHY

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Assessment of Diastolic Filling Indexes Obtained by Radionuclide Ventriculography

Ralph A.H. Stewart and William J. McKenna

Radionuclide ventriculography is a useful technique for the noninvasive assessment of left ventricular diastolic filling. In this study the influence of residual volume and heart rate on different radionuclide indexes of diastolic filling was compared in patients with hypertrophic cardiomyopathy and normal subjects. The peak filling rate, measured in end-diastolic counts, was influenced by the residual volume and failed to detect impaired early diastolic filling in patients with hypertrophic cardiomyopathy. This was suggested by a prolonged time to 30% filling and time to peak filling rate, which were more sensitive measures of impaired early diastolic filling in hypertrophic cardiomyopathy than the first third filling fraction, which was strongly influenced by heart rate, and the peak filling rate measured in stroke volume counts/s, even though this index was not influenced by differences in residual volume. Recognition of the influence of factors other than left ventricular filling on certain radionuclide indexes allows improved selection and interpretation of indexes of left ventricular diastolic filling.

CONGENITAL HEART DISEASE

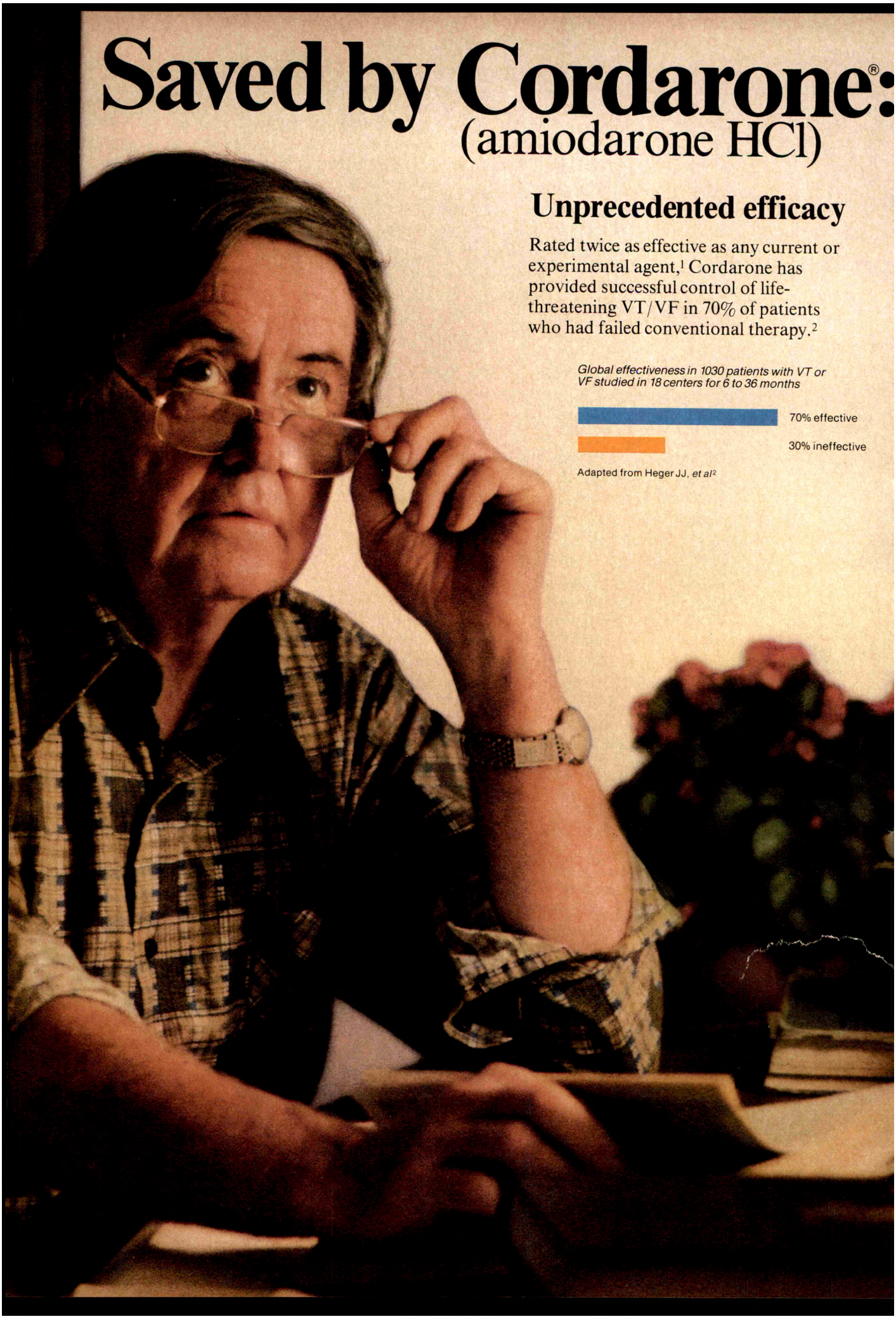
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Characteristics and Natural History of Abnormal Atrial Rhythms in Left Isomerism

Kazuo Momma, Atsuyoshi Takao, and Toshimitsu Shibata

Standard 15-lead electrocardiograms of 50 patients with left isomerism were studied with respect to atrial rhythms. Multiple atrial rhythms were present in 68%, and P waves with superiorly oriented mean frontal axis were present in 98%. Slow P rates (<the second percentile of normal heart rate) or junctional rhythms associated with slowing of atrial rate were recorded in 50%, either persistently or transiently and repeatedly. Slowing of the P rate was progressive. In patients with right isomerism and 5 other congenital heart diseases, slowing of the P rate was only rarely observed.

Continued on page A41

Saved by Cordarone®:
(amiodarone HCl)



Unprecedented efficacy

Rated twice as effective as any current or experimental agent,[1] Cordarone has provided successful control of life-threatening VT/VF in 70% of patients who had failed conventional therapy.[2]

Global effectiveness in 1030 patients with VT or VF studied in 18 centers for 6 to 36 months

Adapted from Heger JJ, *et al*[2]

the most effective antiarrhythmic known to man

...with virtually no effect on LVEF

In contrast to other antiarrhythmics, Cordarone can effectively suppress ventricular arrhythmias in most CHF patients without causing significant adverse hemodynamic effects.[3-5] Oral doses of Cordarone do not depress LVEF during rest or exercise.[6] Occurrence of CHF is uncommon (3%) and rarely requires discontinuation of therapy.

A manageable challenge...

Cordarone® therapy is challenging and may entail frequent side effects that are sometimes potentially serious. Most adverse effects, however, are reversible with dose reduction or discontinuation. Thorough familiarity with the package insert is essential before prescribing Cordarone.

Importantly, Cordarone has virtually no effect on LVEF. Although proarrhythmic potential is associated with all antiarrhythmic agents, proarrhythmic potential of Cordarone is about 2-5%.

...with enduring quality-of-life benefits

Responsive patients are usually controlled with low, once-daily maintenance dosage, often with reduction or elimination of concomitant medication. Exercise tolerance is unchanged or increased,[3] and symptoms such as chest pain and dyspnea often improve in patients with cardiomyopathy.[7]

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Cordarone®
(amiodarone HCl)

See important information on next page.

Cordarone® (amiodarone HCl) Tablets

Indications and Usage: Indicated only for treatment of these documented, life-threatening recurrent ventricular arrhythmias, when they have not responded to documented adequate doses of other antiarrhythmics or when alternative agents could not be tolerated: recurrent ventricular fibrillation, recurrent hemodynamically unstable ventricular tachycardia.

Cordarone© should be used only by physicians familiar with and with access to use of all available modalities for treating recurrent life-threatening ventricular arrhythmias, and access to monitoring facilities, including in-hospital and ambulatory continuous electrocardiographic monitoring and electrophysiologic techniques. Because of the life-threatening nature of arrhythmias treated, potential interactions with prior therapy, and potential exacerbation of arrhythmia, initiation of Cordarone therapy should be in the hospital.

Contraindications: Contraindicated in severe sinus-node dysfunction causing marked sinus bradycardia; second- and third-degree atrioventricular block, and when episodes of bradycardia have caused syncope (except when used with a pacemaker).

Warnings

Cordarone © is intended for use only in patients with the indicated life-threatening arrhythmias because its use is accompanied by substantial toxicity.
Cordarone © has several potentially fatal toxicities, the most important of which is pulmonary toxicity (interstitial pneumonitis/alveolitis) that has resulted in clinically manifest disease at rates as high as 10-15% in some series of patients with ventricular arrhythmias given doses around 400 mg/day, and as abnormal diffusion capacity without symptoms in a much higher percentage of patients. Pulmonary toxicity has been fatal about 10% of the time. Liver injury is common with Cordarone, but is usually mild and evidenced only by abnormal liver enzymes. Overt liver disease can occur, however, and has been fatal in a few cases. Like other antiarrhythmics, Cordarone can exacerbate the arrhythmia, e.g., by making the arrhythmia less well tolerated or more difficult to reverse. This has occurred in 2-5% of patients in various series, and significant heart block or sinus bradycardia has been seen in 2-5%. All of these events should be manageable in the proper clinical setting in most cases. Although the frequency of such proarrhythmic events does not appear greater with Cordarone than with many other agents used in this population, the effects are prolonged when they occur.
Even in patients at high risk of arrhythmic death, in whom the toxicity of Cordarone is an acceptable risk, Cordarone poses major management problems that could be life-threatening in a population at risk of sudden death, so that every effort should be made to utilize alternative agents first.
The difficulty of using Cordarone effectively and safely itself poses a significant risk to patients. Patients with the indicated arrhythmias must be hospitalized while the loading dose of Cordarone is given, and a response generally requires at least one week, usually two or more. Because absorption and elimination are variable, maintenance-dose selection is difficult, and it is not unusual to require dosage decrease or discontinuation of treatment. In a retrospective survey of 192 patients with ventricular tachyarrhythmias, 84 required dose reduction and 18 required at least temporary discontinuation because of adverse effects, and several series have reported 15-20% overall frequencies of discontinuation due to adverse reactions. The time at which a previously controlled life-threatening arrhythmia will recur after discontinuation or dose adjustment is unpredictable, ranging from weeks to months. The patient is obviously at great risk during this time and may need prolonged hospitalization. Attempts to substitute other antiarrhythmic agents when Cordarone must be stopped will be made difficult by the gradually, but unpredictably, changing amiodarone body burden. A similar problem exists when Cordarone is not effective; it still poses the risk of an interaction with whatever subsequent treatment is tried.

PULMONARY TOXICITY: Cordarone© causes a syndrome of progressive dyspnea and cough with functional, radiographic, gallium-scan, and pathological data showing a pulmonary interstitial process, sometimes called alveolitis. Frequency has generally been low (2-7% in most published reports), but recent preliminary reports found 11–15% in patients treated for over a year on average and there is evidence of increasing frequency with time and/or daily or cumulative dose. Although the syndrome is usually reversible when Cordarone is discontinued, with or without steroid therapy, fatalities have occurred in about 10% of cases. Any new respiratory symptom in a patient on Cordarone should suggest possibility of pulmonary toxicity and lead to clinical and radiographic evaluation, with gallium-scan and pulmonary-function evaluation if needed. Particular care should be taken not to presume such symptoms are related to cardiac failure. Again, diffusion capacity appears to be the pulmonary-function test most likely to show abnormality. Evidence of toxicity should lead, at a minimum, to dose reduction, and preferably to drug withdrawal to establish reversibility. In some cases, rechallenge at a lower dose has not resulted in return of toxicity. Periodic chest X-rays and clinical evaluation (every 3-6 months) are recommended and baseline pulmonary-function tests, including diffusion capacity, should be obtained.

WORSENED ARRHYTHMIA: Cordarone© can cause serious exacerbation of the presenting arrhythmia, a risk that may be enhanced by presence of concomitant antiarrhythmics. Exacerbation has been reported in about 2-5% in most series, and has included new ventricular fibrillation, incessant ventricular tachycardia, increased resistance to cardioversion, and polymorphic ventricular tachycardia associated with QT prolongation (Torsade de Pointes). In addition, Cordarone has caused symptomatic bradycardia or sinus arrest with suppression of escape foci in 2-4%.

LIVER INJURY: Elevations of hepatic enzyme levels are frequent in patients on Cordarone and in most cases are asymptomatic. If increase exceeds three times normal, or doubles in a patient with elevated baseline, consider discontinuation of Cordarone or dosage reduction. In a few cases in which biopsy was done, histology resembled that of alcoholic hepatitis or cirrhosis. Hepatic failure has been a rare cause of death in patients on Cordarone.

Precautions: CORNEAL MICRODEPOSITS, IMPAIRMENT OF VISION:
Corneal microdeposits appear in most adults on Cordarone. They are usually discernible only by slit-lamp examination, but give rise to symptoms such as visual halos or blurred vision in up to 10%. Corneal microdeposits are reversible upon dose reduction or termination. Asymptomatic microdeposits are not a reason to reduce dose or discontinue.
PHOTOSENSITIVITY: Cordarone© has induced photosensitization in about 10%; some protection may be afforded by sun-barrier creams or protective clothing. On long-term treatment, blue-gray discoloration of exposed skin may occur. Risk may be increased in patients with fair complexion or excessive sun exposure, and may be related to cumulative dose and duration of therapy.
THYROID ABNORMALITIES: Cordarone© inhibits peripheral conversion of thyroxine (T_4) to triiodothyronine (T_3), tending to cause somewhat increased thyroxine levels and increased levels of inactive reverse T_3, and somewhat decreased levels of T_3. It also is a potential source of large amounts of inorganic iodine.
Cordarone can cause hypothyroidism or hyperthyroidism. Thyroid function should be monitored at baseline and periodically, particularly in any patient with history of thyroid nodules, goiter or other dysfunction. Hypothyroidism has been reported in 2-4% in most series but in 8-10% in others and is probably best identified by a finding of elevated TSH. Hypothyroidism is best managed by Cordarone dose reduction and/or thyroid hormone supplement. However, therapy must be individualized, and it may be necessary to discontinue Cordarone in some patients.
Hyperthyroidism occurs in about 2% of patients receiving Cordarone, but the incidence may be higher among patients with prior inadequate dietary iodine intake. Cordarone-induced hyperthyroidism usually poses a greater hazard to the patient than hypothyroidism because of the possibility of arrhythmia breakthrough or aggravation. In fact, IF ANY NEW SIGNS OF ARRHYTHMIA APPEAR, THE POSSIBILITY OF HYPERTHYROIDISM SHOULD BE CONSIDERED. Hyperthyroidism is best identified by relevant clinical symptoms and signs, accompanied usually by abnormally elevated levels of serum T_3 RIA, and further elevations of serum T_4, and a subnormal serum TSH level (using a sufficiently sensitive TSH assay). The finding of a flat TSH response to TRH is confirmatory of hyperthyroidism and may be sought in equivocal cases. Since arrhythmia breakthroughs may accompany Cordarone-induced hyperthyroidism, aggressive medical treatment is indicated, including, if possible, dose reduction or withdrawal of Cordarone. The institution of antithyroid drugs, beta-adrenergic blockers and/or temporary corticosteroid therapy may be necessary. The action of antithyroid drugs may be especially delayed in amiodarone-induced thyrotoxicosis because of substantial quantities of preformed thyroid hormones stored in the gland. Radioactive iodine therapy is contraindicated because of the low radioiodine uptake associated with amiodarone-induced hyperthyroidism. Experience with thyroid surgery in this setting is extremely limited and this form of therapy runs the theoretical risk of inducing thyroid storm. Cordarone-induced hyperthyroidism may be followed by a transient period of hypothyroidism.
HYPOTENSION POSTBYPASS: Rare occurrences of hypotension upon discontinuation of cardiopulmonary bypass during open-heart surgery in patients on Cordarone have been reported.
LABORATORY TESTS: Elevations in liver enzymes (SGOT and SGPT) can occur. Regularly monitor liver enzymes in patients on relatively high maintenance doses. With persistent significant elevations in liver enzymes or hepatomegaly, consider reducing maintenance dose or discontinuing.
Cordarone© alters the results of thyroid-function tests, causing increase in serum T_4 and serum reverse T_3 and decline in serum T_3. Despite these biochemical changes, most patients remain clinically euthyroid.
DRUG INTERACTIONS: Although only a small number of drug-drug interactions with Cordarone have been explored formally, most of these have shown such an interaction. The potential for other interactions should be anticipated, particularly for drugs with potentially serious toxicity, such as other antiarrhythmics. If such drugs are needed, their dose should be reassessed and, where appropriate, plasma concentration measured. In view of amiodarone's long and variable half-life, potential for drug interactions exists not only with concomitant medication but with drugs administered after discontinuing Cordarone.
Digitalis: Cordarone© in patients on digoxin regularly results in increase in serum digoxin that may reach toxic levels with resultant clinical toxicity. **On initiation of Cordarone, need for digitalis therapy should be reviewed, and the dose reduced by approximately 50% or discontinued.** If digitalis is continued, serum levels should be closely monitored and patients observed for clinical evidence of toxicity. These precautions probably should apply to digitoxin administration as well.
Anticoagulants: Potentiation of warfarin-type anticoagulant response is almost always seen in patients on Cordarone and can result in serious or fatal bleeding. **The dose of the anticoagulant should be reduced by one-third to one-half, and prothrombin times should be monitored closely.**
Antiarrhythmic Agents: Quinidine, procainamide, disopyramide and phenytoin have been used concurrently with Cordarone. There have been reports of increased steady-state levels of quinidine, procainamide and phenytoin during concomitant therapy with Cordarone. In general, any added antiarrhythmic should be initiated at a lower than usual dose with careful monitoring.
Combination of Cordarone with other antiarrhythmic therapy should generally be reserved for patients with life-threatening ventricular arrhythmias who are incompletely responsive to a single agent or incompletely responsive to Cordarone. During transfer to Cordarone the dose levels of previously administered agents should be reduced by 30-50% several days after addition of Cordarone, when arrhythmia suppression should be beginning. The continued need for the other antiarrhythmic agent should be reviewed after the effects of Cordarone have been established, and discontinuation ordinarily should be attempted. If the treatment is continued, these patients should be particularly carefully monitored for adverse effects, especially conduction disturbances and exacerbation of tachyarrhythmias, as Cordarone is continued. In Cordarone patients who require additional antiarrhythmic therapy, the initial dose of such agents should be approximately half the usual recommended dose.
Cordarone© should be used with caution in patients on beta blockers or calcium antagonists because of possible potentiation of bradycardia, sinus arrest and AV block; if necessary, Cordarone can be continued after insertion of a pacemaker in patients with severe bradycardia or sinus arrest.

SUMMARY OF DRUG INTERACTIONS WITH CORDARONE

Concomitant Drug	Interaction		Recommended Dose Reduction of Concomitant Drug
	Onset (days)	Magnitude	
Warfarin	3-4	Increases prothrombin time by 100%	↓1/3-1/2
Digoxin	1	Increases serum concentration by 70%	↓1/2
Quinidine	2	Increases serum concentration by 33%	↓1/3-1/2 (or discontinue)
Procainamide	<7	Increases plasma concentration by 55%; NAPA* concentration by 33%	↓1/3 (or discontinue)

*NAPA = n-acetyl procainamide

ELECTROLYTE DISTURBANCES: Since antiarrhythmic drugs may be ineffective or arrhythmogenic in patients with hypokalemia, correct any potassium or magnesium deficiency before beginning Cordarone.
CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY:
Cordarone© reduced fertility of male and female rats at 90 mg/kg/day (8 times highest recommended human maintenance dose).
Cordarone© caused a statistically significant, dose-related increase in incidence of thyroid tumors (follicular adenoma and/or carcinoma) in rats. Incidence of thyroid tumors was greater than control even at lowest Cordarone level tested, i.e., 5 mg/kg/day or approximately 1/2 the highest recommended human maintenance dose. Mutagenicity studies (Ames, micronucleus and lysogenic tests) with Cordarone were negative.
PREGNANCY: PREGNANCY CATEGORY C: Cordarone© has been shown to be embryotoxic (increased fetal resorption and growth retardation) in rats given orally at 200 mg/kg/day (18 times maximum recommended maintenance dose). Similar findings have been noted in one strain of mice at 5 mg/kg/day (approximately 1/2 the maximum recommended maintenance dose) and higher, but not in a second strain nor in the rabbit at doses up to 100 mg/kg/day (9 times maximum recommended maintenance dose).
Cordarone© should be used during pregnancy only if potential benefit to mother justifies unknown risk to fetus.
LABOR AND DELIVERY: It is not known whether the use of Cordarone during labor or delivery has any immediate or delayed adverse effects.
NURSING MOTHERS: Cordarone© is excreted in human milk, suggesting that breast-feeding could expose the nursing infant to a significant dose. Nursing offspring of lactating rats administered Cordarone have been shown to be less viable and have reduced body-weight gains. Therefore, when Cordarone is indicated, mothers should be advised to discontinue nursing.
PEDIATRIC USE: Safety and effectiveness of Cordarone© in children have not been established.

Adverse Reactions: Adverse reactions have been very common in virtually all series of patients treated with Cordarone for ventricular arrhythmias and with relatively large doses (400 mg/day and above) they occurred in about three fourths of all patients, causing discontinuation in 7-18%. The most serious reactions are pulmonary toxicity, exacerbation of arrhythmia, and rare serious liver injury (See WARNINGS), but other adverse effects constitute important problems. They are often reversible with dose reduction and virtually always reversible with cessation of drug. Most adverse effects appear to become more frequent with continuous treatment beyond six months, although rates appear to remain relatively constant beyond one year. The time and dose relationships of adverse effects are under continued study.
Neurologic problems are extremely common, occurring in 20-40% and include malaise and fatigue, tremor and involuntary movements, poor coordination and gait, and peripheral neuropathy; they are rarely a reason to stop therapy and may respond to dose reductions.
Gastrointestinal complaints, most commonly nausea, vomiting, constipation and anorexia, occur in about 25% but rarely require discontinuation. They commonly occur during high-dose administration (i.e., loading dose) and usually respond to dose reduction or divided doses.
Asymptomatic corneal microdeposits are present in virtually all adult patients who have been on drug for more than 6 months. Some patients develop eye symptoms of halos, photophobia, and dry eyes. Vision is rarely affected and drug discontinuation is rarely needed.
Dermatological adverse reactions occur in about 15% with photosensitivity being most common (about 10%). Sunscreen and protection from sun exposure may be helpful, and drug discontinuation is not usually necessary. Prolonged exposure to Cordarone© occasionally results in a blue-gray pigmentation, slowly and occasionally incompletely reversible on discontinuation of drug but of cosmetic importance only. Cardiovascular adverse reactions, other than exacerbation of arrhythmias, include the uncommon occurrence of congestive heart failure (3%) and bradycardia. Bradycardia usually responds to dosage reduction but may require a pacemaker for control. CHF rarely requires discontinuation. Cardiac conduction abnormalities occur infrequently and are reversible on discontinuation.
The following side-effect rates are based on a retrospective study of 241 patients treated for 2-1,515 days (mean 441.3 days).
The following side effects were each reported in 10-33%: Gastrointestinal: Nausea and vomiting
The following side effects were each reported in 4-9%:
Dermatologic: Solar dermatitis/photosensitivity
Neurologic: Malaise and fatigue, tremor/abnormal involuntary movements, lack of coordination, abnormal gait/ataxia, dizziness, paresthesias
Gastrointestinal: Constipation, anorexia
Ophthalmologic: Visual disturbances
Hepatic: Abnormal liver-function tests
Respiratory: Pulmonary inflammation or fibrosis
The following side effects were each reported in 1-3%:
Thyroid: Hypothyroidism, hyperthyroidism
Neurologic: Decreased libido, insomnia, headache, sleep disturbances
Cardiovascular: Congestive heart failure, cardiac arrhythmias, SA node dysfunction
Gastrointestinal: Abdominal pain
Hepatic: Nonspecific hepatic disorders
Other: Flushing, abnormal taste and smell, edema, abnormal salivation, coagulation abnormalities.
The following side effects were each reported in less than 1%:
Blue skin discoloration, rash, spontaneous ecchymosis, alopecia, hypotension and cardiac conduction abnormalities. Rare occurrences of hepatitis, cirrhosis, optic neuritis, epididymitis, vasculitis, pseudotumor cerebri, and thrombocytopenia have been reported in patients receiving Cordarone. The relationship of these events to Cordarone therapy has not been definitely established.
In surveys of almost 5,000 patients treated in open U.S. studies and in published reports of Cordarone treatment, adverse reactions most frequently requiring discontinuation included pulmonary infiltrates or fibrosis, paroxysmal ventricular tachycardia, congestive heart failure and elevation of liver enzymes. Other symptoms causing discontinuations less often included visual disturbances, solar dermatitis, blue skin discoloration, hyperthyroidism and hypothyroidism.

Overdosage: There have been 3 reported cases of overdose in which 3-8 grams were taken. There were no deaths or permanent sequelae. Animal studies indicate Cordarone© has a high oral LD_{50}(>3,000 mg/kg). In addition to general supportive measures, patient's cardiac rhythm and blood pressure should be monitored, and if bradycardia ensues, a β-adrenergic agonist or a pacemaker may be used. Hypotension with inadequate tissue perfusion should be treated with positive inotropic and/or vasopressor agents. Neither Cordarone nor its metabolite is dialyzable.

Dosage and administration
BECAUSE OF THE UNIQUE PHARMACOKINETIC PROPERTIES, DIFFICULT DOSING SCHEDULE, AND SEVERITY OF THE SIDE EFFECTS IF PATIENTS ARE IMPROPERLY MONITORED, CORDARONE SHOULD BE ADMINISTERED ONLY BY PHYSICIANS EXPERIENCED IN TREATMENT OF LIFE-THREATENING ARRHYTHMIAS WHO ARE THOROUGHLY FAMILIAR WITH RISKS AND BENEFITS OF CORDARONE THERAPY, AND WHO HAVE ACCESS TO LABORATORY FACILITIES CAPABLE OF ADEQUATELY MONITORING EFFECTIVENESS AND SIDE EFFECTS OF TREATMENT. To ensure an antiarrhythmic effect will be observed without waiting several months, loading doses are required. A uniform, optimal dosage schedule for Cordarone has not been determined. Individual patient titration is suggested according to following guidelines.
For life-threatening ventricular arrhythmias, e.g., ventricular fibrillation or hemodynamically unstable ventricular tachycardia: Close monitoring of the patient is indicated during loading phase, particularly until risk of recurrent ventricular tachycardia or fibrillation has abated. Because of serious nature of the arrhythmia and lack of predictable time course of effect, loading should be performed in a hospital setting. Loading doses of 800-1,600 mg/day are required for 1-3 weeks (occasionally longer) until initial therapeutic response occurs. (Administration of Cordarone in divided doses with meals is suggested for total daily doses of 1,000 mg or higher, or when gastrointestinal intolerance occurs.) If side effects become excessive, dose should be reduced. Elimination of recurrence of ventricular fibrillation and tachycardia usually occurs within 1-3 weeks, along with reduction in complex and total ventricular ectopic beats. Upon starting Cordarone, attempt should be made to gradually discontinue prior antiarrhythmic drugs (see section on "Drug Interactions"). When adequate arrhythmia control is achieved, or if side effects become prominent, Cordarone dose should be reduced to 600-800 mg/day for one month and then to the maintenance dose, usually 400 mg/day (See "Clinical Pharmacology"-"Monitoring Effectiveness" in package insert). Some patients may require larger maintenance doses, up to 600 mg/day, and some can be controlled on lower doses. Cordarone© may be administered as a single daily dose, or in patients with severe gastrointestinal intolerance, as a b.i.d. dose. In each patient, the chronic maintenance dose should be determined according to antiarrhythmic effect as assessed by symptoms, Holter recordings, and/or programmed electrical stimulation and by patient tolerance. Plasma concentrations may be helpful in evaluating nonresponsiveness or unexpectedly severe toxicity. (See "Clinical Pharmacology" in package insert).
The lowest effective dose should be used to prevent occurrence of side effects. In all instances, the physician must be guided by severity of individual patient's arrhythmia and response to therapy. When dosage adjustments are necessary, patient should be closely monitored for an extended period of time because of long and variable half-life of Cordarone and difficulty in predicting time required to attain new steady-state level. Dosage suggestions are summarized below:

	Loading Dose (Daily)	Adjustment and Maintenance Dose (Daily)	
	1-3 weeks	~1 month	usual maintenance
Ventricular Arrhythmias	800-1,600 mg	600-800 mg	400 mg

Consult full package insert before use.

How Supplied: 200 mg tablets, bottles of 60 and REDIPAK© cartons of 100.

Manufactured for **Wyeth Laboratories Inc.**, Philadelphia, PA 19101 by **Sanofi, S.A.**, Paris, France, by arrangement with **Sanofi Pharmaceuticals, Inc.**

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MISCELLANEOUS

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Doppler Echocardiographic-Determined Changes in Left Ventricular Diastolic Filling Flow Velocity During the Lower Body Positive and Negative Pressure Method
Toshiyuki Takahashi, Masahiko Iizuka, Hiroshi Sato, Takashi Serizawa, Shin-ichi Momomura, Takatoshi Mochizuki, Osami Kohmoto, Teruhiko Aoyagi, Hiroshi Matsui, Hiroshi Ikenouchi, Tsuguya Sakamoto, and Tsuneaki Sugimoto

We analyzed changes in Doppler-derived parameters of left ventricular (LV) diastolic filling flow and hemodynamic variables during the lower body positive and negative pressure method, which has 5 steps. The peak velocity of LV early diastolic filling flow and mean pulmonary capillary wedge pressure changed stepwise with lower body pressure in an almost parallel fashion. The peak velocity of LV late diastolic filling flow was less changed during the procedures. Changes in pulmonary wedge pressure correlated with those in the peak velocity of LV early diastolic filling flow during lower body pressure of −20 mm Hg. These data suggest that left atrial pressure is one of the important determinants of LV early diastolic filling in this setting.

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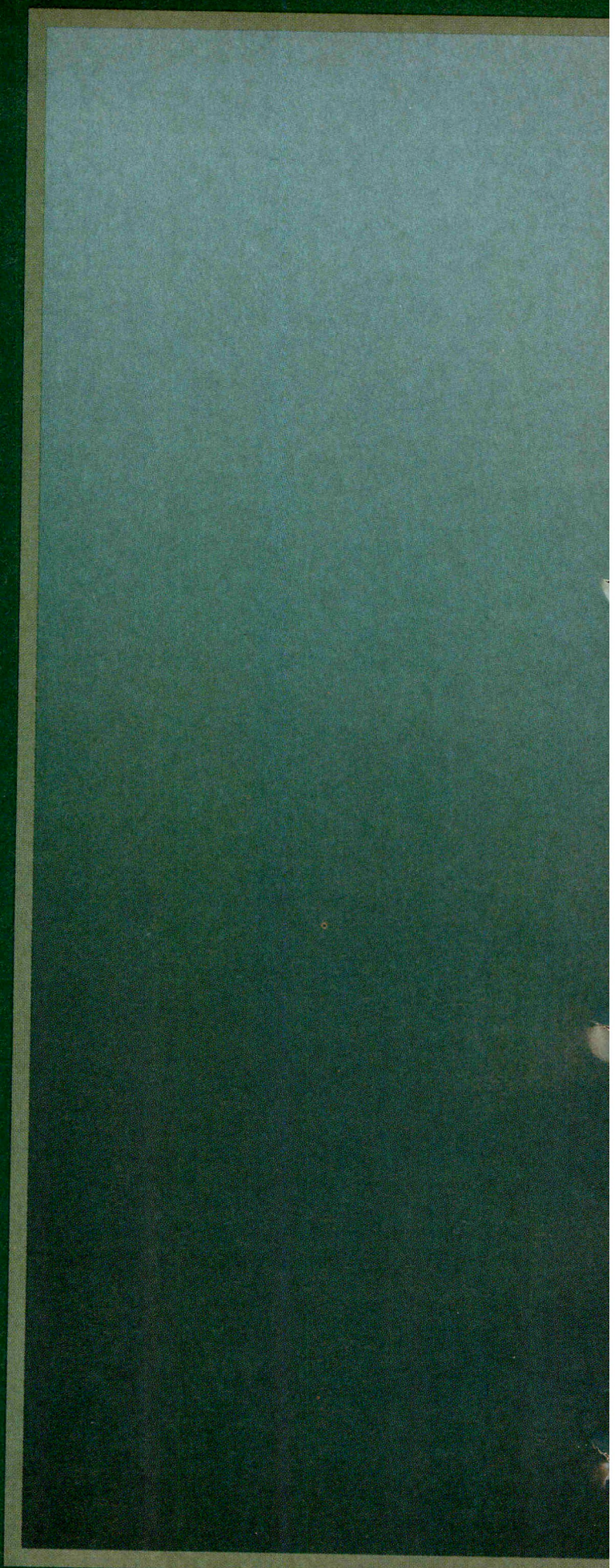
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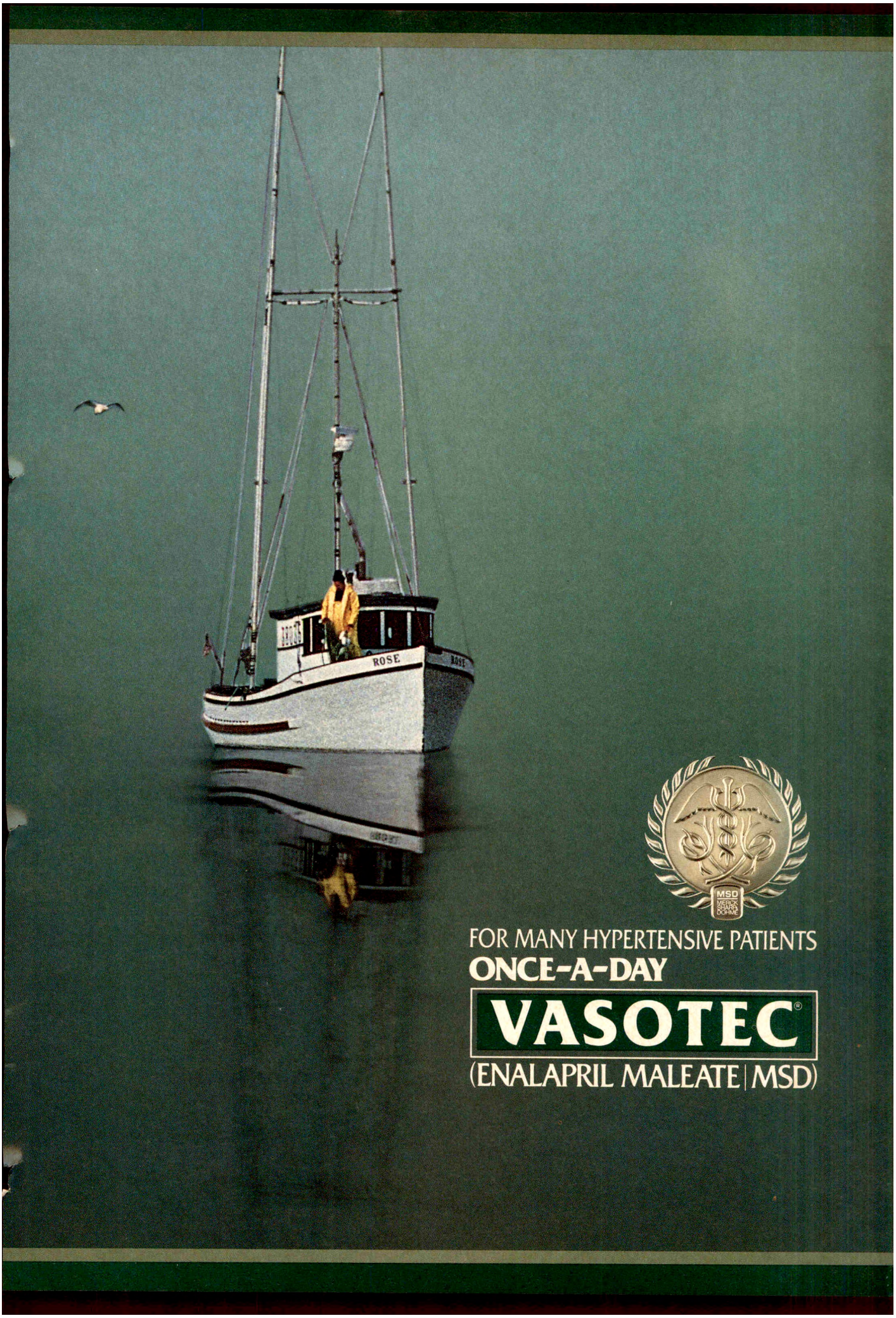
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Warnings: *Angioedema:* Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with ACE inhibitors, including VASOTEC. In such cases, VASOTEC should be promptly discontinued and the patient carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL), should be promptly administered.** (See ADVERSE REACTIONS.)

Hypotension: Excessive hypotension is rare in uncomplicated hypertensive patients treated with VASOTEC alone. Patients with heart failure given VASOTEC commonly have some reduction in blood pressure, especially with the first dose, but discontinuation of therapy for continuing symptomatic hypotension usually is not necessary when dosing instructions are followed; caution should be observed when initiating therapy. (See DOSAGE AND ADMINISTRATION.) Patients at risk for excessive hypotension, sometimes associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death, include those with the following conditions or characteristics: heart failure, hyponatremia, high-dose diuretic therapy, recent intensive diuresis or increase in diuretic dose, renal dialysis, or severe volume and/or salt depletion of any etiology. It may be advisable to eliminate the diuretic (except in patients with heart failure), reduce the diuretic dose, or increase salt intake cautiously before initiating therapy with VASOTEC in patients at risk for excessive hypotension who are able to tolerate such adjustments. (See PRECAUTIONS, *Drug Interactions* and ADVERSE REACTIONS.) In patients at risk for excessive hypotension, therapy should be started under very close medical supervision and such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart disease or cardiovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident. If excessive hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses of VASOTEC, which usually can be given without difficulty once the blood pressure has stabilized. If symptomatic hypotension develops, a dose reduction or discontinuation of VASOTEC or concomitant diuretic may be necessary.

Neutropenia/Agranulocytosis: Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Foreign marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Precautions: *General: Impaired Renal Function:* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including VASOTEC, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when VASOTEC has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or VASOTEC may be required.

Evaluation of patients with hypertension or heart failure should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION.)

Hyperkalemia: Elevated serum potassium (>5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. In clinical trials in heart failure, hyperkalemia was observed in 3.8% of patients, but was not a cause for discontinuation.

Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with VASOTEC. (See *Drug Interactions.*)

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients:

Angioedema: Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness, especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with enalapril is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions:

Hypotension: Patients on Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide close medical supervision after the initial dose for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

Agents Causing Renin Release: The antihypertensive effect of VASOTEC is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents: VASOTEC has been used concomitantly with beta-adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine, prazosin, and digoxin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium: VASOTEC attenuates potassium loss caused by thiazide-type diuretics. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. Potassium-sparing agents should generally not be used in patients with heart failure receiving VASOTEC.

Lithium: Lithium toxicity has been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. A few cases of lithium toxicity have been reported in patients receiving concomitant VASOTEC and lithium and were reversible upon discontinuation of both drugs. It is recommended that serum lithium levels be monitored frequently if enalapril is administered concomitantly with lithium.

Pregnancy – Category C: There was no fetotoxicity or teratogenicity in rats treated with up to 200 mg/kg/day of enalapril (333 times the maximum human dose). Fetotoxicity, expressed as a decrease in average fetal weight, occurred in rats given 1200 mg/kg/day of enalapril but did not occur when these animals were supplemented with saline. Enalapril was not teratogenic in rabbits. However, maternal and fetal toxicity occurred in some rabbits at doses of 1 mg/kg/day or more. Saline supplementation prevented the maternal and fetal toxicity seen at doses of 3 and 10 mg/kg/day, but not at 30 mg/kg/day (50 times the maximum human dose).

Radioactivity was found to cross the placenta following administration of labeled enalapril to pregnant hamsters.

There are no adequate and well-controlled studies of enalapril in pregnant women. However, data are available that show enalapril crosses the human placenta. Because the risk of fetal toxicity with the use of ACE inhibitors has not been clearly defined, VASOTEC® (Enalapril Maleate, MSD) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Postmarketing experience with all ACE inhibitors thus far suggests the following with regard to pregnancy outcome. Inadvertent exposure limited to the first trimester of pregnancy has not been reported to affect fetal outcome adversely. Fetal exposure during the second and third trimesters of pregnancy has been associated with fetal and neonatal morbidity and mortality.

When ACE inhibitors are used during the later stages of pregnancy, there have been reports of hypotension and decreased renal perfusion in the newborn. Oligohydramnios in the mother has also been reported, presumably representing decreased renal function in the fetus. Infants exposed *in utero* to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion with the administration of fluids and pressors as appropriate. Problems associated with prematurity such as patent ductus arteriosus have occurred in association with maternal use of ACE inhibitors, but it is not clear whether they are related to ACE inhibition, maternal hypertension, or the underlying prematurity.

Nursing Mothers: Milk in lactating rats contains radioactivity following administration of ^{14}C enalapril maleate. It is not known whether this drug is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when VASOTEC is given to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Adverse Reactions: VASOTEC has been evaluated for safety in more than 10,000 patients, including over 1000 patients treated for one year or more. VASOTEC has been found to be generally well tolerated in controlled clinical trials involving 2987 patients.

HYPERTENSION: The most frequent clinical adverse experiences in controlled trials were: headache (5.2%), dizziness (4.3%), and fatigue (3%).

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in controlled clinical trials were: diarrhea (1.4%), nausea (1.4%), rash (1.4%), cough (1.3%), orthostatic effects (1.2%), and asthenia (1.1%).

HEART FAILURE: The most frequent clinical adverse experiences in both controlled and uncontrolled trials were: dizziness (7.9%), hypotension (6.7%), orthostatic effects (2.2%), syncope (2.2%), cough (2.2%), chest pain (2.1%), and diarrhea (2.1%).

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in both controlled and uncontrolled clinical trials were: fatigue (1.8%), headache (1.8%), abdominal pain (1.6%), asthenia (1.6%), orthostatic hypotension (1.6%), vertigo (1.6%), angina pectoris (1.5%), nausea (1.3%), vomiting (1.3%), bronchitis (1.3%), dyspnea (1.3%), urinary tract infection (1.3%), rash (1.3%), and myocardial infarction (1.2%).

Other serious clinical adverse experiences occurring since the drug was marketed or adverse experiences occurring in 0.5% to 1% of patients with hypertension or heart failure in clinical trials in order of decreasing severity within each category:

Cardiovascular: Cardiac arrest; myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high-risk patients (see WARNINGS, *Hypotension*); cardiac arrest; pulmonary embolism and infarction; rhythm disturbances; atrial fibrillation; palpitation.

Digestive: Ileus, pancreatitis, hepatitis or cholestatic jaundice, melena, anorexia, dyspepsia, constipation, glossitis, stomatitis.

Musculoskeletal: Muscle cramps.

Nervous/Psychiatric: Depression, confusion, ataxia, somnolence, insomnia, nervousness, paresthesia.

Urogenital: Renal failure, oliguria, renal dysfunction (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Respiratory: Bronchospasm, rhinorrhea, sore throat and hoarseness, asthma, upper respiratory infection.

Skin: Herpes zoster, urticaria, pruritus, alopecia, flushing, hyperhidrosis.

Special Senses: Blurred vision, taste alteration, tinnitus.

A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgias/arthritis, myalgias, fever, serositis, vasculitis, leukocytosis, eosinophilia, photosensitivity, rash, and other dermatologic manifestations.

Angioedema: Angioedema has been reported in patients receiving VASOTEC (0.2%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Hypotension: In the hypertensive patients, hypotension occurred in 0.9% and syncope occurred in 0.5% of patients following the initial dose or during extended therapy. Hypotension or syncope was a cause for discontinuation of therapy in 0.1% of hypertensive patients. In heart failure patients, hypotension occurred in 6.7% and syncope occurred in 2.2% of patients. Hypotension or syncope was a cause for discontinuation of therapy in 1.9% of patients with heart failure. (See WARNINGS.)

Clinical Laboratory Test Findings:

Serum Electrolytes: Hyperkalemia (see PRECAUTIONS), hyponatremia.

Creatinine, Blood Urea Nitrogen: In controlled clinical trials, minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.2% of patients with essential hypertension treated with VASOTEC alone. Increases are more likely to occur in patients receiving concomitant diuretics or in patients with renal artery stenosis. (See PRECAUTIONS.) In patients with heart failure who were also receiving diuretics with or without digitalis, increases in blood urea nitrogen or serum creatinine, usually reversible upon discontinuation of VASOTEC and/or other concomitant diuretic therapy, were observed in about 11% of patients. Increases in blood urea nitrogen or creatinine were a cause for discontinuation in 1.2% of patients.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g% and 1.0 vol %, respectively) occur frequently in either hypertension or heart failure patients treated with VASOTEC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia.

Other (Causal Relationship Unknown): In marketing experience, rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported. A few cases of hemolysis have been reported in patients with G6PD deficiency.

Liver Function Tests: Elevations of liver enzymes and/or serum bilirubin have occurred.

Dosage and Administration: *Hypertension:* In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally may occur following the initial dose of VASOTEC. The diuretic should, if possible, be discontinued for two to three days before beginning therapy with VASOTEC to reduce the likelihood of hypotension. (See WARNINGS.) If the patient's blood pressure is not controlled with VASOTEC alone, diuretic therapy may be resumed.

If the diuretic cannot be discontinued, an initial dose of 2.5 mg should be used under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, *Drug Interactions.*)

The recommended initial dose in patients not on diuretics is 5 mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range is 10 to 40 mg per day administered in a single dose or in two divided doses. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. In such patients, an increase in dosage or twice-daily administration should be considered. If blood pressure is not controlled with VASOTEC alone, a diuretic may be added.

Concomitant administration of VASOTEC with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium (see PRECAUTIONS).

Dosage Adjustment in Hypertensive Patients with Renal Impairment: The usual dose of enalapril is recommended for patients with a creatinine clearance > 30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with creatinine clearance ≤ 30 mL/min (serum creatinine ≥ 3 mg/dL), the first dose is 2.5 mg once daily. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

Heart Failure: VASOTEC is indicated as adjunctive therapy with diuretics and digitalis. The recommended starting dose is 2.5 mg once or twice daily. After the initial dose of VASOTEC, the patient should be observed under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, *Drug Interactions.*) If possible, the dose of the diuretic should be reduced, which may diminish the likelihood of hypotension. The appearance of hypotension after the initial dose of VASOTEC does not preclude subsequent careful dose titration with the drug, following effective management of the hypotension. The usual therapeutic dosing range for the treatment of heart failure is 5 to 20 mg daily given in two divided doses. The maximum daily dose is 40 mg. Once-daily dosing has been effective in a controlled study, but nearly all patients in this study were given 40 mg, the maximum recommended daily dose, and there has been much more experience with twice-daily dosing. In addition, in a placebo-controlled study which demonstrated reduced mortality in patients with severe heart failure (NYHA Class IV), patients were treated with 2.5 to 40 mg per day of VASOTEC, almost always administered in two divided doses. (See CLINICAL PHARMACOLOGY, *Pharmacodynamics and Clinical Effects.*) Dosage may be adjusted depending upon clinical or hemodynamic response. (See WARNINGS.)

Dosage Adjustment in Patients with Heart Failure and Renal Impairment or Hyponatremia: In patients with heart failure who have hyponatremia (serum sodium < 130 mEq/L) or with serum creatinine >1.6 mg/dL, therapy should be initiated at 2.5 mg daily under close medical supervision. (See DOSAGE AND ADMINISTRATION, *Heart Failure,* WARNINGS, and PRECAUTIONS, *Drug Interactions.*) The dose may be increased to 2.5 mg b.i.d., then 5 mg b.i.d. and higher as needed, usually at intervals of four days or more, if at the time of dosage adjustment there is not excessive hypotension or significant deterioration of renal function. The maximum daily dose is 40 mg.

For more detailed information, consult your MSD Representative or see Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486. J9VS54R(818)

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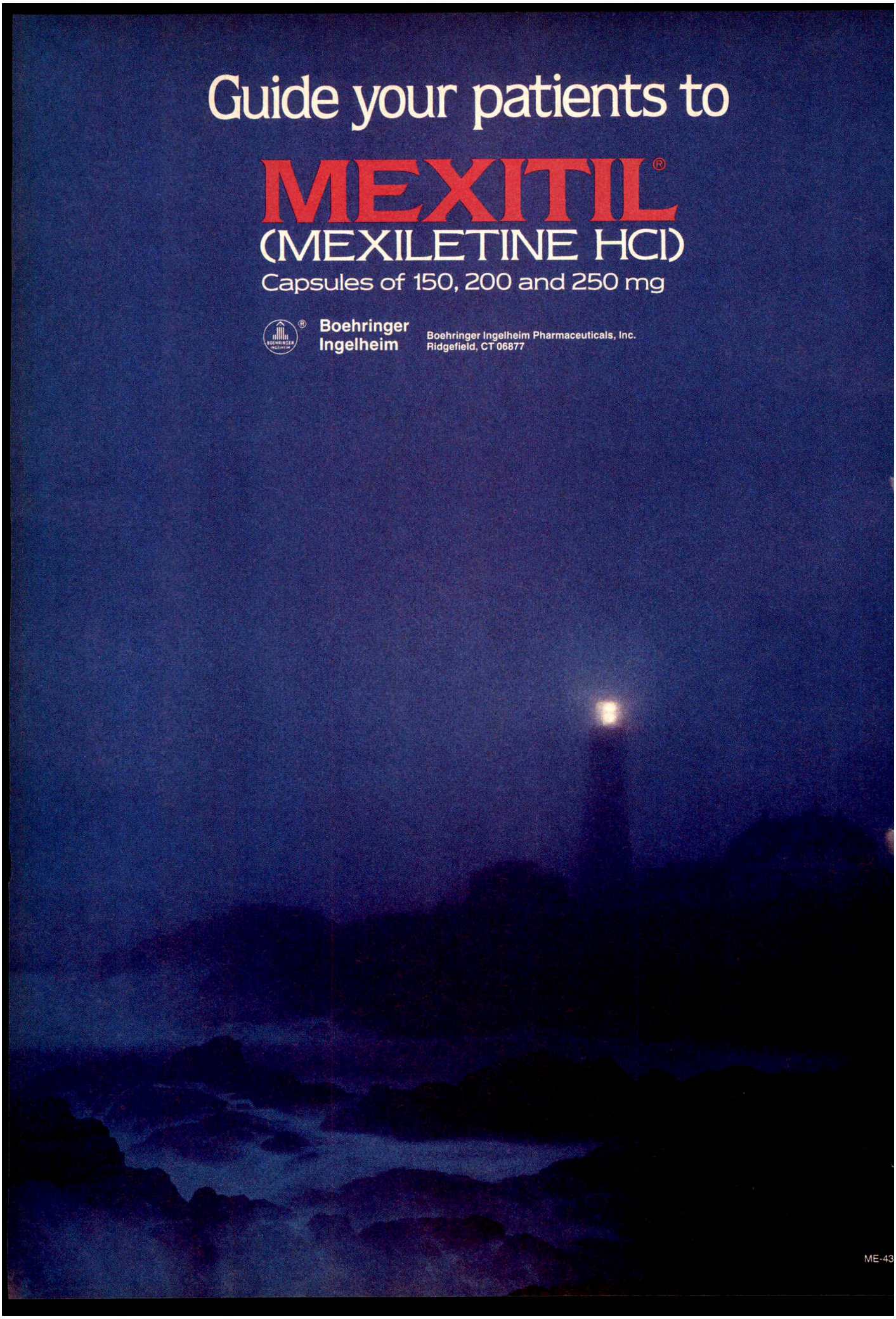
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JANUARY 15, 1990, VOL. 65, NO. 3

A Double-Blind Randomized Multicenter Dose-Ranging Trial of Intravenous Streptokinase in Acute Myocardial Infarction

A. Jacob Six, MD, Hans W. Louwerenburg, MD, Reinier Braams, MD, Karel Mechelse, MD, Willem L. Mosterd, MD, Ad C. Bredero, MD, Peter H.J.M. Dunselman, MD, and Norbert M. van Hemel, MD*

Intravenous streptokinase administration is now a widely applied therapy for patients in the early hours of acute myocardial infarction (AMI). The dosages used do not appear to be based on comparative clinical investigations. Therefore a double-blind randomized trial was carried out to establish the optimal dose of streptokinase. A total of 189 patients who had symptoms of AMI for <4 hours were treated with 200,000, 750,000, 1,500,000 or 3,000,000 IU streptokinase intravenously. At coronary angiography 2.8 ± 2.7 hours (mean ± standard deviation) after the start of streptokinase infusion, patency of the infarct-related coronary artery was observed in 38, 75, 60 and 82% of the patients, respectively, in the 4 groups. The result of the dosage of 200,000 IU was significantly poorer than that of the other dosages ($p < 0.01$). The result of a dosage of 3,000,000 IU was significantly better than that of 1,500,000 IU ($p < 0.05$), but the differences with 750,000 IU were not significant. Blood transfusion was required in 4 patients (2%), distributed over the 4 groups in 0, 2, 1 and 1 of the patients. One patient had major bleeding; this patient had been treated with 750,000 IU. The 3-month mortality-rate in the whole study population was 5%. Thus, of the 4 doses of streptokinase tested, 750,000 IU is the minimal therapeutic dosage, and the arguments for 1,500,000 IU as standard therapy for comparison with other fibrinolytic drugs are poor. The best results in this study were achieved with 3,000,000 IU, but further research will be needed to establish the efficacy and safety of this new regimen.

(Am J Cardiol 1990;65:119–123)

From St. Antonius Hospital, Nieuwegein, Gaubius Institute TNO, Leiden, Lichtenberg Hospital, Amersfoort, St. Ignatius Hospital, Breda, and Diakonessenhuis, Utrecht, the Netherlands. This study was supported in part by a grant from Kabi Inc., Stockholm, Sweden. Manuscript received June 29, 1989; revised manuscript received and accepted September 6, 1989.

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*See Appendix.

It has been clearly established that intravenous administration of streptokinase in the early phase of acute myocardial infarction (AMI) results in recanalization of the infarct-related coronary artery, salvage of left ventricular function and reduction of mortality.[1] Intravenous streptokinase administration as a treatment for AMI has been applied since the early 1960s, but it required long-term infusion of millions of units during several hours or days. After the good results of intracoronary administration of streptokinase, the intravenous infusion was reintroduced, but now as a short-term, high-dose infusion in the early hours of AMI.[2] This new application of streptokinase was not preceded by investigations of dose-response relations, as normally required for the introduction of new drugs. Schröder et al[2] proposed the infusion of 1,500,000 IU streptokinase in 1 hour, based on their clinical experiences. This dosage became generally accepted and was applied in various studies.[1] In this double-blind, multicenter trial, we investigated the effects of several dosages of intravenous streptokinase to establish the dose-response for efficacy and safety.

METHODS

Patients: Between March 1986 and August 1987, 189 patients were included in the trial. The number of patients recruited in each center was 87 patients in Amersfoort, 19 in Breda, 40 in Nieuwegein and 33 in Utrecht. Male and female patients under 71 years of age who, on admission to the coronary care unit, had had symptoms of AMI for >30 minutes and <4 hours, whose symptoms could not be relieved by sublingual isosorbide dinitrate and who had ST-segment elevations of at least 1 mm in 2 of the 12 leads of the electrocardiogram, were considered for inclusion.

Exclusion criteria were any defect in hemostasis, including the use of anticoagulant drugs, recent surgery, history of cerebrovascular accident or recent trauma of the central nervous system, known severe renal insufficiency, blood pressure >200 mm Hg systolic or 120 mm Hg diastolic, severe heart failure with pulmonary congestion on admission, malignancies except those of the skin and previous treatment with streptokinase.

The patients and their relatives, if present, received a written and verbal explanation of the trial and gave ver-

TABLE I Baseline Characteristics of Patients in the Four Groups

Group	A	B	C	D	Total
Streptokinase dose × 1,000 IU	200	750	1,500	3,000	
Total no. of patients	27	54	56	52	189
Age (yrs)	58 ± 7	57 ± 9	56 ± 10	56 ± 10	57 ± 9
Male gender (%)	25	47	47	43	162 (86)
Cigarette smoker (%)	17	41	42	34	134 (71)
Systolic blood pressure on admission (mm Hg)	137 ± 23	138 ± 28	137 ± 26	142 ± 22	139 ± 25
Diastolic blood pressure on admission (mm Hg)	79 ± 12	86 ± 16	89 ± 18	89 ± 14	88 ± 15
Localization of ST elevations (%)					
Anterior	7	17	22	14	60 (32)
Inferior	9	18	13	19	59 (31)
Lateral and combinations	11	19	21	19	70 (37)
Sum of ST elevations (%)					
<2 mm	0	1	0	1	2 (1)
2 to <5 mm	9	14	8	7	38 (20)
5 to <10 mm	6	17	16	17	56 (30)
>10 mm	12	22	32	27	93 (49)

All ± data are mean ± standard deviation.

bal consent in presence of a member of the nursing staff. The study protocol had been accepted by the ethical committee and was considered in agreement with the Helsinki Declaration.

Treatment: Every participating coronary care unit disposed of numbered boxes containing 4 apparently identical ampoules together with either 200,000 (group A), 750,000 (group B), 1,500,000 (group C) or 3,000,000 (group D) IU streptokinase (Kabikinase®; provided by Kabi Inc.). The contents were dissolved in 50 ml of saline, and infused in 1 hour in a brachial vein using an infusion pump. The allocation number was noted on all sheets of the patient form. The infusion was immediately stopped in case of any allergic reaction or bleeding complication or decrease of the systolic blood pressure to <100 mm Hg. Steroid prophylaxis was not given.

Angiography: Within 4 hours after the start of the infusion, coronary angiography was performed by Sones or Judkins technique. During the catheterization, 5,000 IU of heparin was administered, and 2.5 mg of isosorbide dinitrate was given sublingually. Angiography of the right coronary artery was done in at least 2 projections and the branches of the left coronary artery in at least 3. Coronary angiography was filmed on 35 mm cinefilm. The films were subsequently forwarded to the central core angiographic laboratory to be assessed by cardiologists specializing in coronary angiography. This assessment was the primary endpoint of the study.

Assessment of coronary angiograms: Each angiogram was analyzed by 2 pairs of experienced independent cardiologists, blinded to clinical data apart from the electrocardiogram on admission. In the few cases where assessment differed, the film was reviewed again in the presence of the complete angiography assessment committee until consensus was achieved. The following data were coded: the probable infarct-related coronary artery segment described following the recommendations of the World Health Organization,[3] a visual estimation of the diameter reduction, the coronary segment that was involved and the degree of perfusion following the classification that was proposed by the Thrombolysis in Myocardial Infarction study group (grade 0 = no perfusion, grade 1 = penetration with minimal perfusion, grade 2 = partial perfusion and grade 3 = complete perfusion; detailed definitions are given by Sheehan et al).[4] "Patent" was defined as Thrombolysis in Myocardial Infarction grade II or III. The patency was classified on the first angiogram of the infarction-related artery. The extent of coronary artery disease was noted as 0-, 1-, 2- or 3-vessel disease. In a poor quality angiogram, patency was not classified.

Anticoagulant regimen: After the catheterization the patient was taken back to the coronary care unit, where heparin infusion was started at a dosage of 1,000 IU/hour and adjusted according to activated partial thromboplastin time determinations twice daily (aimed values 1.5 to 2 × control), until adequate anticoagulation with acenocoumarol, started on the day of admission, was achieved. Coumarin was continued for at least 3 months. Blood transfusions were given in case of a decrease of hemoglobin concentration below 6.0 mM/liter. If necessary, hypovolemia could be treated by infusion of plasma substitutes.

Follow-up treatment: All medication was noted on the trial form. Antiarrhythmic drugs were not given routinely. Salicylates were not prescribed. Analgesic drugs were given freely. Blood pressure, complications and all known side effects were followed during the clinical treatment. After 3 months the patient was seen at the outpatient department. Examination consisted of patient history, medication review, measurement of blood pressure and heart rate, electrocardiography and measurement of the ejection fraction by radionuclide ventriculography with technetium-99m-labeled red blood cells.

Laboratory investigations: Immediately before the start of the infusion and 24 hours thereafter, hemoglobin concentration and hematocrit were determined. Creatine phosphokinase and creatine phosphokinase-MB were determined before infusion, after 12 hours and after 24 hours, followed by determinations once

daily until they had returned to normal values. In a selected number of patients, blood samples were taken by specialized laboratory personnel before streptokinase infusion and during heart catheterization. Blood was drawn after minimal venous congestion and after the first milliliters of blood had been discarded. Samples were collected in 0.1 volume citrate-containing plastic tubes, immediately placed in ice, centrifuged at 4°C, "snap" frozen and stored at −70°C for later analysis at the Gaubius Institute TNO in Leiden, the Netherlands.

Data collection and statistics: All data except the streptokinase dosage were collected by means of a coding form that was designed before the advance of the trial and that included relevant guidelines. Data handling and statistical analysis were centralized and carried out independently of the investigators as well as Kabi Inc. Correctness and concordance of the data were both checked. The data analysis was performed with SPSS-PC (SPSS Inc.). Statistical significance was assessed with the *t* test. Two-tailed values were calculated. A p value <0.05 was considered significant. Differences were calculated at 95% confidence limits. Continuous variables were presented as mean ± standard deviation.

RESULTS

Patients: Baseline characteristics of the patients in the 4 groups are listed in Table I. No significant differences were found between the 4 groups.

Angiographic data: In 9 of the 189 patients (5%) no angiogram was available for reviewing. In 4 patients angiography was not performed, as events such as ventricular tachycardia (1), transient ischemic attack (1) or allergic reactions (2) had occurred. In 1 patient the catheterization procedure could not be completed due to a dissection of the iliac artery. Two patients refused to undergo catheterization and in 2 cases the catheterization room was not available.

An interim analysis was performed on the angiographic data received until December 31, 1986 (91 patients).[5] Because patency in the 200,000 IU group appeared to be significantly lower ($p<0.01$) than that of the 3 other groups, randomization to this dose was discontinued for ethical reasons. At the completion of the study, patency was demonstrated in group A, B, C and D in 38.4, 75.0, 60.3 and 81.6% of the patients, respectively. The confidence limits of these values are: 18 to 56% for group A, 65 to 89% for group B, 47 to 74% for group C and 71 to 93% for group D. The difference between the patency rates in group C and D is significant ($p<0.05$); the difference between group B and C and between group B and D are not. A dose-response curve is shown in Figure 1. The detailed classification of coronary flow is listed in Table II.

Time delay: The delay between onset of the symptoms and start of the therapy was 2.5 ± 1.6 hours, and was approximately equal in the 4 groups (2.7 ± 2.4, 2.4 ± 1.0, 2.7 ± 2.1 and 2.4 ± 0.9 hours, respectively). The delay from start of infusion until angiography amounted on average to 2.8 ± 2.9, 2.8 ± 2.4, 3.0 ± 3.6 and 2.4 ± 1.1 hours, respectively; the association with patency rates is listed in Table III. The maximal patency rate was observed when angiography was performed 2 to 3 hours after the start of streptokinase infusion.

TABLE II Coronary Angiography (Perfusion Grade as per the TIMI Study)

Group	A	B	C	D	Total B,C,D
Streptokinase dose × 1,000 IU	200	750	1,500	3,000	
TIMI 0 (%)	10	10	16	6	32 (21)
TIMI I (%)	6	3	5	3	11 (7)
TIMI II (%)	3	6	4	6	16 (10)
Patency rate (%)	38*	75	60	82†	72
TIMI III (%)	7	33	28	34	95 (62)
Subtotal	26	52	53	49	154
Perfusion not classified (%)	1	2	3	3	8 (5)
Total	27	54	56	52	162

* Patency in group A is significantly lower than in the other 3 groups; † patency in group D is significantly higher than in group C. The other differences are not significant. For explanation of TIMI classification see Methods.
TIMI = Thrombolysis in Myocardial Infarction.

TABLE III Patency Rates in the Four Groups Stratified for the Time Interval Between the Start of Streptokinase Infusion Until Coronary Angiography

Group	A	B	C	D	
Streptokinase dose × 1,000 IU	200	750	1,500	3,000	Total
No. of hours angiography performed after start streptokinase (%)					
1	20	—	67	50	33
1 to 2	25	70	62	71	65
2 to 3	—	82	63	95	80
>3	60	75	50	80	67
Total (%)	38	75	60	82	67

Complications and side effects: One patient in group A had a temporary hematemesis. One patient in group B had severe bleeding in the lumbar spine, a few hours after the catheterization, with partial paralysis of the legs. One patient in group C had a retroperitoneal hematoma, and a large hematoma at the puncture site,

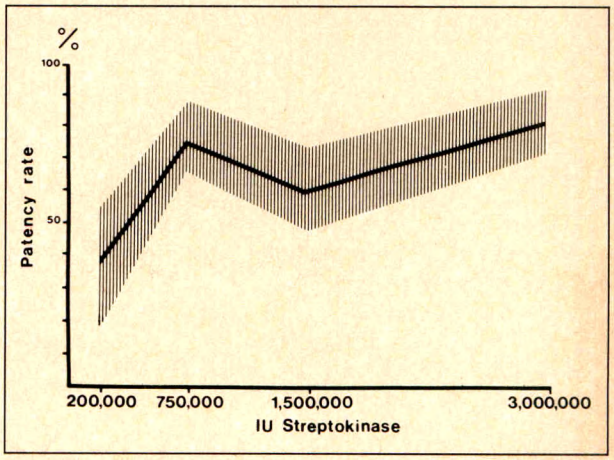


FIGURE 1. Association between the dosage of streptokinase and patency rates at angiography 2.8 ± 2.7 hours (mean ± standard deviation) after the start of the infusion. The *drawn line* represents the mean patency of the 4 groups. The *shaded area* shows 95% confidence limits.

requiring blood transfusion. Streptokinase infusion was stopped in 1 other patient in group C, because of a loss of consciousness 15 minutes after the start of the infusion with complete recovery at neurologic examination within 1 hour. The reaction was classified as a transient ischemic attack. Larger hematomas at the puncture site occurred in 7, 9, 10 and 13% of the patients in the 4 groups. Cerebral hemorrhage or hemopthysis did not occur. The total number of patients having ≥1 major complication was 6 (3%).

A slight reduction in systolic blood pressure during streptokinase infusion was observed in all groups (mean decrease 13.9 ± 15.6% in the total population, and 10.1 ± 11.0, 10.4 ± 18.1, 11.8 ± 11.4 and 21.8 ± 16.6% in groups A through D, respectively); the difference between group C and D is significant ($p = 0.011$); the other differences are not significant. However, because no decrease in the systolic blood pressure to <100 mm Hg occurred, infusion of plasma was not required.

Follow-up: In 15 patients (8%) significant Q-wave formation did not occur: 1 patient in group A (4%), 5 in group B (9%), 4 in group C (7%) and 5 in group D (10%).

During the 3-month follow-up period 10 patients (5%) died: 2 in group A (7%), 2 in group B (4%), 3 in group C (5%) and 3 in group D (6%) (difference not significant). Two patients have gone abroad; they are thought to be alive. Reinfarction during the hospital stay occurred in 17 patients (8.9%): 0 in group A, 4 in group B (8%), 7 in group C (13%) and 6 in group D (12%). Reinfarction occurred on average after 3.7 ± 2.0 days. Thirty-seven patients had percutaneous transluminal coronary angioplasty, 4 in group A, 8 in group B, 15 in group C and 10 in group D. Coronary bypass surgery had been performed in 10 patients: 2 in group A, 3 in group B, 2 in group C and 3 in group D.

The global ejection fractions at 3-month radionuclide ventriculography were 48 ± 18, 50 ± 14, 45 ± 16 and 48 ± 11%, respectively. These differences are not significant. The average ejection fraction in patients with a patent coronary artery was significantly higher than in patients with permanent occlusion: 49 ± 16 versus 43 ± 13 ($p < 0.025$).

DISCUSSION

At present intravenous streptokinase infusion is a widely used therapy for patients with AMI. A mortality reduction of 25 to 80% after administration of 1,500,000 IU has been established.[1] Surprisingly, the dose selection for large studies has not been based on conventional dose-ranging studies.

Published clinical data: Few clinical data on dose-response relations are available. Lew et al[6] retrospectively investigated the influence of the rate of infusion of 750,000 IU on noninvasive signs of reperfusion, and concluded that higher rates of infusion lead to earlier reperfusion, but this effect seems to level off at 500 IU/kg/min.[6] Gottlich et al[7] described a prospective study in 56 patients in which the influence of 3 different dosages of streptokinase (500,000, 750,000 and 1,500,000 IU) on time intervals from onset of pain to peak creatine kinase and on the consumption of fibrinogen were measured. This study failed to demonstrate increasing efficacy with increasing dosages. However, noninvasive tests such as creatine kinase peaking have a very limited—if any—predictive value for angiographically proven recanalization.[8] The same criticisms hold true for 2 other studies.[9,10] Col et al[11] published a more extensive study on 135 patients with an acute myocardial infarction, 83 of whom received either 500,000 IU or 1,500,000 IU streptokinase intravenously. They demonstrated a higher amount of "activator" in the circulation after infusion of the higher dosage, but found similar patency rates at coronary angiography after about 555 ± 260 minutes (range 2 to 24 hours).

In vitro investigations: In vitro investigations—which can give only rough approximations of the system in vivo—showed a bell-shaped dose-work curve, indicating a dose optimum.[12–15] Furthermore, it appears that the main determinant of the solubility of a clot is its composition and not the choice of the fibrinolytic drug, provided that the concentration is sufficient.[16] This gives further credit to the hypothesis that a higher concentration of streptokinase or streptokinase-plasminogen complex on the clot surface will result in a higher extent of penetration of the agent into the clot and thus the degree of successful thrombolysis.[17]

Studies in animals: Animals are generally not suitable for the evaluation of fibrinolytic drugs, in particular with streptokinase, as the fibrinolytic system and the occurrence of streptokinase-neutralizing antibodies are different from species to species.[18,19]

Dose-response curve: Because this double-blind dose-ranging study included 4 fixed dosages, 4 measured points of a dose-response curve are available. Obviously, differences in patency rates could be in part due to random deviation. Therefore 95% confidence limits are represented as the shaded area in Figure 1. This random deviation allows multiple interpretations of the curve. On one hand this curve seems to be 2-topped. On the other hand, this result does not exclude the possibility of a sigmoidal dose-effect relation with a steep leg between 200,000 and 750,000 IU and a certain leveling-off at higher dosages.

Differences between dosages: Of the 4 doses tested, 750,000 IU is the minimal therapeutic dose. However, intravenous administration of 200,000 IU appears to give some therapeutic result when comparing the achieved patency rate of 38% with the 10 to 20% patency rate that is seen when no fibrinolytic drugs are given.[20,21] The patency rate after 1,500,000 IU is similar to that after 750,000 IU (difference not significant) and significantly lower than after 3,000,000 IU ($p < 0.05$). A major consequence of this finding is that trials comparing newer fibrinolytic drugs with the infusion of 1,500,000 IU streptokinase[4,22,23] have a limited impact, as these trials compare at least 1 drug at a suboptimal dosage. The best result in our trial is achieved with 3,000,000 IU. Newer studies are required to establish efficacy (in terms of left ventricular preservation and mortality reduction) and safety of this regimen. As an 82% patency rate may be close to what can be achieved

with any thrombolytic intervention, and a somewhat greater reduction in blood pressure was found with 3,000,000 IU, it does not appear to be desirable to include even higher doses of streptokinase if a new dose-ranging study is planned.

Complications: The rate of complications was low: 1 patient (0.5%) had neurologic complications causing permanent disabilities, blood transfusion was required in 2% of the patients and 3-month mortality was 5%. The bleeding rate after streptokinase does not appear to be dose-related, as is the case with tissue plasminogen activator.[24]

Time delay: The design of this dose-finding study resembles that of the European Cooperative Study, comparing the intravenous infusion of 1,500,000 IU streptokinase with 0.75 mg of tissue plasminogen activator.[22] In that study streptokinase infusion resulted in a 55% patency rate. Our somewhat better overall patency rate of 72% with the 3 higher dosages may be explained in part by the greater delay between the start of infusion and angiography (2.8 ± 2.7 vs 1.25 to 1.5 hours in the European Cooperative Study). The occurrence of patency is maximal at angiography after 2 to 3 hours (Table III). It may be argued that differences in patency rates between the 4 groups are not only related to dosages, but also (in view of the fact that all dosages were given in 1 hour) to infusion rates, which were doubled both from group B to C and from group C to D. Limited experiences with higher infusion rates are available from published studies. Hellstern et al[9] demonstrated that high dosages of streptokinase in patients with acute myocardial infarction were well tolerated.

Clinical implications: It is established that, of the 4 doses tested, 750,000 IU is the minimal therapeutic dosage of streptokinase. The arguments for considering the infusion of 1,500,000 IU streptokinase as a "standard therapy" for comparison with other fibrinolytic drugs are poor. The best results in the present study were achieved with 3,000,000 IU, but further research will be needed to establish the efficacy and safety of this new regimen.

Acknowledgment: All residents who performed the entry inclusion procedure during day and night are gratefully acknowledged.

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APPENDIX

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Results of High Dose Intravenous Urokinase for Acute Myocardial Infarction

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To determine the outcome of patients after treatment with high-dose intravenous urokinase (3 million U) 102 patients were prospectively evaluated in the setting of acute myocardial infarction. The first 61 patients received intravenous urokinase as a continuous infusion and the last 41 patients were treated with an initial 1.5 million U intravenous bolus. Sixty-two percent of all patients had patent infarct-related arteries by the time of immediate angiography (median time 2.2 hours), which was performed in all patients. There was no significant difference in patency rates between patients treated with or without an initial intravenous bolus. Twenty-eight (28%) patients developed clinical evidence of recurrent ischemia (death, reocclusion, emergency angioplasty, urgent bypass surgery) during hospitalization, whereas only 7 (7%) developed angiographically documented reocclusion. Of 28 patients who failed to achieve successful reperfusion at the time of immediate catheterization, rescue angioplasty was technically successful in establishing reperfusion in all but 1 patient. No significant improvement in median global left ventricular function was seen between immediate (48%) and follow-up catheterization (48%). Significant bleeding complications were unusual except in 1 patient who experienced an intracranial hemorrhage. Eight (8%) patients died during hospitalization. Therefore, the use of high-dose intravenous urokinase in patients with acute myocardial infarction is associated with a 62% patency rate, a low incidence of reocclusion and bleeding complications and a high technical success rate with rescue angioplasty at the time of immediate catheterization. This study supports the need for further randomized controlled trials comparing intravenous urokinase directly with other thrombolytic regimens.

(Am J Cardiol 1990;65:124–131)

Successful reperfusion with intravenous thrombolytic therapy in acute myocardial infarction (AMI) has been associated with an improvement in global left ventricular function, decreased in-hospital and long-term mortality and decreased congestive heart failure after infarction.[1–4] Despite this apparent success, recurrent ischemia and reocclusion remain the "Achilles heel" of thrombolytic therapy.[5–8] Previous studies evaluating intravenous urokinase suggest that this problem may be substantially decreased when this agent is used as monotherapy or in combination with recombinant tissue plasminogen activator.[9,10] Despite this potentially important initial finding, only 2 studies have previously evaluated intravenous urokinase as monotherapy in this setting,[9,11] and only 1 study has used the currently recommended intravenous dose of 3 million U.

Although these studies demonstrated successful reperfusion in a large proportion of patients and a tendency toward lower rates of recurrent ischemia and reocclusion compared with other thrombolytic agents, the combined experience represents only 308 patients. Therefore, this study was undertaken to evaluate the effects of high-dose intravenous urokinase in establishing perfusion and sustained patency of infarct-related arteries in the setting of AMI, and to determine whether further comparative, controlled trials of a dose of 3 million U of intravenous urokinase would be merited.

METHODS

Patient selection: Patients were prospectively identified in North Carolina community hospitals that collaborate with Duke University Medical Center in thrombolytic trials.[12] Inclusion criteria were: (1) chest pain or equivalent symptoms for ≥30 minutes' duration consistent with coronary ischemia unresponsive to standard sublingual nitroglycerin therapy; (2) onset of chest dis-

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See Appendix for Collaborating Centers.

comfort ≤6 hours of the time of therapy; (3) ST-segment elevation of ≥0.1 mV in at least 2 of 3 inferior leads (II, III and aVF) or at least 2 of 6 precordial leads (V_1 to V_6) or leads I and AVL, or ST-segment depression of the precordial leads (V_1 to V_4) consistent with posterior injury, or in the presence of left bundle branch block, primary ST-segment changes in the inferior or anterior leads; (4) age of ≤75 years; and (5) the willingness and ability to give informed consent for participation in the study. Exclusion criteria included: history of significant bleeding diathesis; history of gastrointestinal or genitourinary bleeding within the preceding 4 weeks; stroke within the past 6 months; major surgery on internal organs during the previous 14 days; uncontrolled hypertension with diastolic blood pressure >110 mm Hg on serial measurements in the emergency room; other serious advanced illnesses likely to severely limit the patient's life expectancy; cardiogenic shock defined as a systolic blood pressure <85 mm Hg unresponsive to volume expanders; previous Q-wave AMI in the acutely ischemic region; prolonged (>10 minutes) cardiopulmonary resuscitation within the previous 2 weeks; severe trauma within the past 6 months; psychological or physical inability to participate in the study; women known to be or suspected of being pregnant. The protocol was approved by the institutional review board at each of the clinical sites.

Thrombolytic therapy administration: In this study, the low molecular weight form of urokinase (Abbott) was used. A total of 3 million U was infused over a 45- to 60-minute period. In the first 61 patients enrolled, urokinase was continually infused without an initial bolus. In the last 41 patients, a bolus of 1.5 million U was administered over 5 minutes with the remaining 1.5 million U infused over the subsequent 45 to 60 minutes. No patient received intravenous heparin in the emergency room but aspirin, 325 mg, was administered orally at the time of thrombolytic therapy initiation.

Cardiac catheterization and coronary angioplasty: After initiation of thrombolytic therapy, patients were transferred to the cardiac catheterization laboratory, where angiography of the infarct-related vessel was performed as closely as possible to 90 minutes after initiation of urokinase, but not before the 90-minute period unless the patient was in hemodynamic distress. Arterial access was obtained via the femoral or brachial route. Five thousand units of intravenous heparin were administered once access was established. At 90 minutes, a minimum of 4 angiograms in various orthogonal and hemiaxial views was obtained. In addition, angiography of the noninfarct-related vessels and the left ventricle was also performed.

Coronary blood flow of the infarct-related vessel was graded according to the Thrombolysis in Myocardial Infarction classification.[13] The final angiographic injection determined triage for angioplasty. Patients who remained consistently occluded at 90 minutes (grade 0 or 1) were eligible for acute coronary angioplasty, which was performed at the discretion of the individual angiographer. In patients with grade 2 flow, acute coronary angioplasty was performed only if there was ongoing evidence of ischemia (chest pain, presence of collaterals or >0.1 mV of persistent ST-segment elevation). In the absence of these characteristics, angioplasty was deferred until predischarge catheterization or until the patient developed clinical evidence of recurrent ischemia (emergency angioplasty). In patients who underwent angioplasty during the acute catheterization, 5,000 additional units of heparin were administered intravenously.

Intracoronary urokinase in a dose of 6,000 U/min for up to 2 hours was used in patients with angiographically visible filling defects suggesting the presence of residual thrombus after angioplasty, marked diminution of flow in the infarct-related artery with imminent reclosure or abrupt closure of the artery after angioplasty or evidence of distal embolization as recognized by angiographic pruning. To monitor the progress of intracoronary thrombolysis, angiographic injections were repeated at 15-minute intervals during the urokinase infusion.

Medical therapy: After immediate catheterization, patients were transferred to the coronary care unit where they received standard therapy with lidocaine, oxygen, morphine as needed for pain and nitrates either topically or intravenously. Aspirin, 325 mg/day, was also administered along with a continuous infusion of intravenous heparin to maintain the partial thromboplastin time at 2 times the control value for our laboratory. This infusion was maintained until repeat cardiac catheterization at 7 to 10 days was accomplished. Beta blockers were not added to the medical regimen unless the patient had previously been treated with them or required such therapy for control of hypertension, supraventricular tachyarrhythmias or noncardiac disorders (e.g., migraine headache). Patients also were treated with calcium antagonists using either diltiazem at 60 mg orally 3 times daily or nifedipine at 20 mg orally 3 times daily. Other medications, including antiarrhythmic agents, were given at the discretion of the clinician. However, no other antiplatelet agents such as dipyridamole were used routinely.

Repeat catheterization and revascularization: Patients underwent repeat cardiac catheterization at 7 to 10 days after infarction even if they had an interim urgent catheterization study or if they had undergone coronary artery bypass grafting. The follow-up study was performed to determine late patency of the infarct-related vessel as well as residual left ventricular function. Coronary angioplasty of the infarct-related vessel was performed during repeat catheterization when there was evidence of a significant residual stenosis suitable for angioplasty, especially if the patient had a positive exercise study. Patients with either severe multivessel disease or lesions of the infarct-related vessel not amenable to angioplasty underwent elective coronary artery bypass surgery before discharge. Emergency surgery was performed for failed angioplasty, particularly if there was evidence of ongoing ischemia with a large amount of myocardium at risk.

Bleeding and coagulation variables: Bleeding observed during the hospital stay was defined as follows: *minor* if it was of no clinical consequence, did not require a transfusion and was <250 cc total blood loss;

TABLE I Baseline Characteristics

Age (yrs)*	52/59/67
Male sex (%)	83
Coronary risk factors† (%)	
Diabetes mellitus	15
Systemic hypertension	48
Hyperlipidemia	24
Cigarette smoking	51
Prior acute myocardial infarction (%)	16
Systolic blood pressure*	120/130/158
Heart rate (beats/min)	64/75/91
Time to treatment (hours)*	1.9/2.8/3.6
Infarct artery (%)	
Left main	1
Left anterior descending	32
Left circumflex	15
Right	50
Graft	2
Multivessel disease (%)	53
Mitral regurgitation (%)	12

* Figures shown are median (25th/50th/75th percentile); † risk factors obtained from admission history. Definitions have been published previously.[31]

moderate if 250 to 500 cc of observed blood loss was noted; *severe* if there was >500 cc of blood loss necessitating a transfusion; or *life-threatening*, which included intracranial bleeding or gastrointestinal or other internal or external bleeding causing hypotension and necessitating emergency transfusion. The site of bleeding, baseline and nadir hematocrit as well as units of packed red blood cells transfused were recorded for all patients.

Blood samples were collected on 0.01 M citrate and 200 kIU/ml aprotinin at baseline, 4 hours and 24 hours after initiation of thrombolytic therapy and were immediately processed and kept frozen at −20°C until assayed by the coagulation laboratory. Fibrinogen was determined by a coagulation rate assay. Fibrinogen degradation products were analyzed by the tanned red cell agglutination inhibition technique at the core hematology laboratory at the University of Vermont. These techniques have previously been described.[14]

Angiographic and ventriculographic analysis: All cineangiograms were evaluated by qualitative and quantitative methods by the angiographic laboratory. Qualitative analysis included coronary angiographic morphology, Thrombolysis in Myocardial Infarction perfusion grade and visual percent stenosis of the infarct-related vessel. This analysis was performed by at least 2 angiographers who were blinded to clinical outcome and were only aware of the designated infarct-related vessel. Quantitative analysis included minimum lumen diameter, percent area stenosis and percent diameter stenosis. This procedure was performed by a cardiologist and technician who were also blinded to patient outcome. The analysis was obtained from cine film using a computerized radiographic automated edge detection method.[15] Details of this technique and our experience with its use have previously been reported.[8,16]

Global left ventricular function was determined by the area length method and expressed as ejection fraction.[17] Regional wall motion of the infarct zone and noninfarct zone was quantified as standard deviations/cord by means of the centerline cord method.[18] Technically inadequate studies due to lack of adequate contrast or frequent ventricular extrasystoles were not included in the analysis.

TABLE II Coronary Patency Rates

Time to Treatment (Hours)	First Injection*	Final Diagnostic Injection
0–2 (%)	16/29 (55)	19/29 (66)
2–4 (%)	30/54 (56)	31/54 (57)
>4 (%)	11/15 (73)	11/15 (73)
Total (%)	57/98 (58)	61/98 (62)

* Median time to first injection was 2.2 hours.

Data analysis: For descriptive purposes, results are expressed as percentages for discrete variables and median (25th to 75th percentiles) for continuous variables.

Case report forms were completed by the clinical research nurse coordinators and reviewed by the principal investigators before submission to the Data Coordinating Center in the Duke Cardiovascular Disease Databank. The data were verified independently by study monitors from review of the clinical records. A data monitoring board met regularly during the study to review the outcome of each patient and to ensure the safety of the ongoing trial. Bleeding complications were monitored carefully by clinical research nurses who reviewed each patient's status on a daily basis.

RESULTS

Patients: Selected baseline clinical and angiographic characteristics of our population are listed in Table I. Of particular note, 53% of patients had multivessel (2- or 3-vessel) disease.

Patency of the infarct-related vessel: The median time from treatment to the first coronary injection was 2.2 hours. Overall, 58% of patients were open at 90 minutes and 62% were open at the time of the final diagnostic injection (Table II). In patients treated >4 hours from the time of symptom onset, 73% were open at 90 minutes as opposed to 55% who were treated within 2 hours. Final infarct-related artery patency rates for patients receiving either the intravenous infusion only or the bolus and infusion were not different. At the final diagnostic injection, 62% of the infusion-only patients had patent infarct-related arteries, compared with 63% of patients treated with bolus and infusion. Of note, only 2 (2%) patients received intracoronary urokinase (750,000 U/patient) at the time of immediate catheterization.

Recurrent ischemia and reocclusion: Twenty-eight of the 102 patients (28%) had recurrent ischemia before follow-up catheterization. Of these, 10 (10%) underwent emergency coronary angioplasty, 14 (14%) were sent to urgent (<7 days) bypass surgery and six patients (7%) experienced reocclusion within the 7-day period. Two (2%) patients experienced recurrent infarction defined by a recurrent elevation of creatine phosphokinase isoenzymes.

Coronary angioplasty: During the course of the hospitalization, 48 patients underwent 56 coronary angio-

TABLE III Angioplasty Results

	Successful* (%)	Partial Success† (%)	Failed (%)
Acute angioplasty‡			
Patent vessel before angioplasty (n = 10)	70	0	30
Occluded vessel before angioplasty (n = 28)	82	14	4
Emergency angioplasty§			
Patent vessel before angioplasty (n = 4)	100	0	0
Occluded vessel before angioplasty (n = 6)	33	67	0
Elective angioplasty			
Patent vessel before angioplasty (n = 7)	86	0	14
Occluded vessel before angioplasty (n = 1)	100	0	0

* Successful = Thrombolysis in Myocardial Infarction grade 3, residual stenosis <60%.
† Partial success = unchanged or improved Thrombolysis In Myocardial Infarction grade and residual stenosis <60% or reduction in stenosis >20%.
‡ Acute angioplasty = time of immediate catheterization.
§ Emergency angioplasty = time of recurrent ischemia.

TABLE IV Left Ventricular Function

	All Patients (n = 63)*	Failed Lysis (n = 26)*	Successful Lysis (n = 35)*
Left ventricular			
Ejection fraction (%)			
Baseline	40/48/54†	44/49/55	39/48/54
Follow-up	40/48/54	41/48/53	40/49/56
EF change	−6/0/5	−5.5/−1/3.5	−6/1/9
Infarct zone			
Regional wall motion (SD/chord)			
Baseline	−3.5/−3.1/−2.3	−3.5/−3.1/−2.3	−3.7/−3.0/−2.3
Follow-up	−3.2/−3.0/−1.7	−3.1/−3.0/−2.0	−3.2/−3.0/−1.5
RWM	−0.25/0.35/0.98	−0.40/0.20/0.8	−0.10/0.40/1.5
Noninfarct zone			
Regional wall motion (SD/chord)			
Baseline	−0.50/0.20/0.70	−0.03/0.40/0.93	−1.0/−0.10/0.70
Follow-up	−0.70/0.0/0.90	−0.38/0.20/0.93	−0.90/0.0/0.90

* Baseline and follow-up values are only for paired observations.
† Figures are shown as median (25th/50th/75th percentile).
EF = ejection fraction; RWM = regional wall motion; SD = standard deviation.

plasty procedures (Table III). In 38 patients the procedure was performed emergently at the time of immediate catheterization. The procedure was successful in 82% of those occluded and partially successful in 14%. Ten patients had angioplasty as an emergency procedure due to recurrent ischemia or reocclusion. Eight patients had an elective angioplasty at the time of routine follow-up catheterization.

Left ventricular function: The results of reperfusion therapy on baseline and follow-up left ventricular function are listed in Table IV. Baseline median ejection fraction for successfully reperfused patients was 48% compared with 49% in those who failed to reperfuse with thrombolytic therapy. Global left ventricular ejection fraction showed no significant change at the 7- to 10-day follow-up study even in those patients who achieved successful thrombolysis. However, improvement in infarct zone regional wall motion was seen in both groups. Noninfarct zone regional wall motion showed a tendency toward mild hypercontractility both at baseline and follow-up in the failed thrombolysis group.

Bleeding complications: The hematocrit and hemostatic parameters are listed in Table V. The median change in hematocrit from the time of presentation for all 102 patients was 12 points, to a nadir hematocrit of 30. The baseline fibrinogen level was 2.8 g/liter in all patients and the nadir fibrinogen was 0.4 g/liter and the peak fibrin degradation products were 720 μg/ml (Figure 1).

Most bleeding complications were mild and occurred at periaccess sites. Nine percent of patients had major (>500 cc) blood loss. One patient (1%) had an intracranial hemorrhage, which resulted after prolonged resuscitation for recurrent ventricular fibrillation in the catheterization laboratory.

Major clinical outcomes: The major clinical outcomes for all patients versus those with and without successful perfusion of the infarct-related artery at the time of acute diagnostic angiography are compared in Table VI. During the course of the hospitalization, 8 patients (8%) died. Five of these deaths were secondary to power failure, 2 were sudden death related to arrhythmias and 1 was secondary to an intracranial hemorrhage. Three of the patients who died had 3-vessel disease, 1 had 2-vessel disease and 4 had 1-vessel disease.

Of particular note, 5 of the 41 (12%) patients who did not have patent arteries at the time of the 90-minute angiogram died in-hospital compared with 3 of the 57 patients (5%) who were successfully reperfused. Reoc-

TABLE V Hematologic Parameters

	All Patients (n = 102)	Nonsurgical Patients (n = 69)
Baseline hematocrit*	40/43/46	40/44/46
Nadir hematocrit*	25/30/34	29/33/35
Hematocrit*	10/12/17	9/11/13
Transfusion ≥2 units	46%	23%
Baseline fibrinogen (g/liter)*	2.3/2.8/3.6	2.3/2.8/3.7
Nadir fibrinogen (g/liter)*	0.18/0.4/0.56	0.18/0.4/0.54
Nadir platelets (K)*	129/161/205	148/168/206
Peak FDP (μg/ml)*	370/720/1350	370/720/1220
Moderate bleeding (n)		
Genitourinary	1	1
Gastrointestinal	4	2
Groin	7	4
Other	2	0
Hematocrit drop only	19	12
Severe and life-threatening bleeding (n)		
Gastrointestinal	1	0
Intracranial	1	1
Groin	3	0
Brachial	1	0
Other	3	1
Hematocrit drop only	5	2

* Figures shown are median (25th/50th/75th percentile).
FDP = fibrin(ogen) degradation products.

clusion occurred in 10% of patients with an initially closed infarct vessel, which was slightly more than the reocclusion rate of 5% seen in the patent group. The reinfarction rate in both groups was somewhat lower than the reocclusion rate. All patients who reoccluded or experienced reinfarction had recurrent ST-segment elevation. None of the recurrent events were silent, with 80% of patients experiencing chest discomfort consistent with recurrent infarction and 1 patient who experienced hypotension. Of all the patients experiencing such events, only 2 were associated with reinfarction with reelevation of cardiac enzymes. Sustained hypotension and ventricular fibrillation were more common in patients who failed to reperfuse. At the time of the predischarge catheterization only 6% of patients had an occluded infarct vessel and 8% were dead, whereas 49% of patients had a patent infarct artery, 30% had a patent bypass graft and 8% did not undergo follow-up catheterization.

DISCUSSION

The major finding of this study is that high-dose intravenous urokinase can be administered in the community hospital setting with an efficacy profile characterized by an overall patency rate of 62% and a low reocclusion rate (<7%). The bleeding risk appears to be comparable to other currently available intravenous agents such as streptokinase and recombinant tissue plasminogen activator. This pilot study of 102 patients adds to the small published database describing the use of high-dose intravenous urokinase in acute myocardial infarction.

The 90-minute patency rate of 62% after intravenous urokinase compares quite favorably with the re-

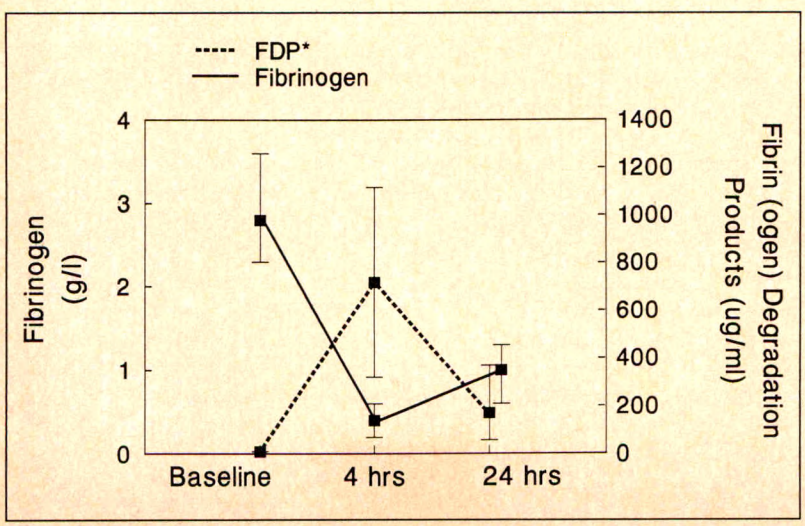


FIGURE 1. Median (25th to 75th percentile) values for fibrinogen and fibrinogen degradation products at baseline evaluation, 4 hours and 24 hours after high dose intravenous urokinase therapy. FDP = fibrinogen degradation products.

ported experience with intravenous streptokinase (35 to 60%) and is very similar to the 66% rate demonstrated with a comparable dose of urokinase in the German Activator Urokinase Study.[9,13,19,20] However, unlike the German Activator Urokinase Study results, patients treated early from symptom onset (≤2 hours) did not achieve a higher perfusion rate (55%) compared to those treated later than 4 hours (73%). These perfusion rates for urokinase are still inferior to the "ceiling" rate of 75% patency demonstrated in Thrombolysis and Angioplasty in Myocardial Infarction-1 and other studies with high-dose recombinant tissue plasminogen activator as well as in Thrombolysis and Angioplasty in Myocardial Infarction-2, where incremental doses of both agents in combination were evaluated (Figure 2).[5,10] Based on results of previous animal studies, we anticipated more rapid and successful reperfusion acutely when 50% of the total drug was given as a bolus over a 5-minute period (W. Barker, personal communication, Abbott Laboratories). Our results do not support this hypothesis, although our sample size is actually too small to securely rule out such an effect.

Recurrent ischemia as defined by the occurrence of death, reocclusion, emergency angioplasty or urgent coronary bypass surgery was quite frequent, occurring in 28% of all patients enrolled. This rate is somewhat higher than the 16% rate observed with combination therapy with recombinant tissue plasminogen activator and urokinase in the Thrombolysis and Angioplasty in Myocardial Infarction-2 trial, but is more consistent with studies evaluating recombinant tissue plasminogen activator only, in which the recurrent ischemia rate has ranged from 25 to 28%.[5,10,21,22] Vigilant patient monitoring by our coronary care staff, who have much previous experience in thrombolytic trials, may partially explain this high detection rate. In previous studies, many angiographically documented reocclusions were reported to be clinically "silent,"[23] leading to an increase in the intensity of monitoring at our institution. The fact that only 2 out of all our patients who reoccluded experienced recurrent infarction supports this speculation.

Despite the high rate of recurrent ischemia, reocclusion occurred in only 7% of patients. This low rate is consistent with previous reports of reocclusion rates using urokinase and lower than the reocclusion rates observed in most trials of recombinant tissue plasminogen activator therapy alone.[5,9,11,22] In addition, patients who failed to reperfuse initially and underwent "rescue" angioplasty to achieve vessel patency had a relatively low rate of reocclusion (10%) in this study; a 29% reocclusion rate was observed in patients treated with "rescue" angioplasty after recombinant tissue plasminogen activator monotherapy.[5] This low reocclusion rate after "rescue" angioplasty in conjunction with urokinase is quite similar to the 7% rate observed with the combination of recombinant tissue plasminogen activator and urokinase therapy in the Thrombolysis and Angioplasty in Myocardial Infarction-2 study and the 7% rate after streptokinase.[10,20] Because acute and follow-up angiography have not been performed in the large trials evaluating intravenous streptokinase without the use of angioplasty, reocclusion rates in the absence of angioplasty with this agent are difficult to assess.[1,2]

The lower rate of reocclusion with or without angioplasty seen with urokinase may be secondary to the more extensive fibrinogen depletion and increased production of fibrin and fibrinogen degradation products demonstrated in this study.[11] As previously suggested by animal and patient studies, fibrin and fibrinogen degradation products may inhibit platelet aggregation and decrease blood viscosity.[24–26] Finally, our aggressive

TABLE VI Major Clinical Outcomes

	All Patients (n = 102)	TIMI GRADE 0 or 1 at Immediate Cath (n = 41)	Patent (TIMI 2 or 3) at Immediate Cath (n = 57)
	(%)	(%)	(%)
Death	8.0	12.0	5.0
Reocclusion	7.0	10.0	5.0
Restenosis	8.0	10.0	5.0
Reinfarction	2.0	2.0	4.0
New pulmonary edema	18.0	15.0	21.0
Heart failure	23.0	22.0	25.0
Sustained hypotension	18.0	24.0	14.0
Ventricular fibrillation	12.0	15.0	11.0
Stroke	2.0	2.0	2.0

Cath = catheterization; TIMI = Thrombolysis in Myocardial Infarction.

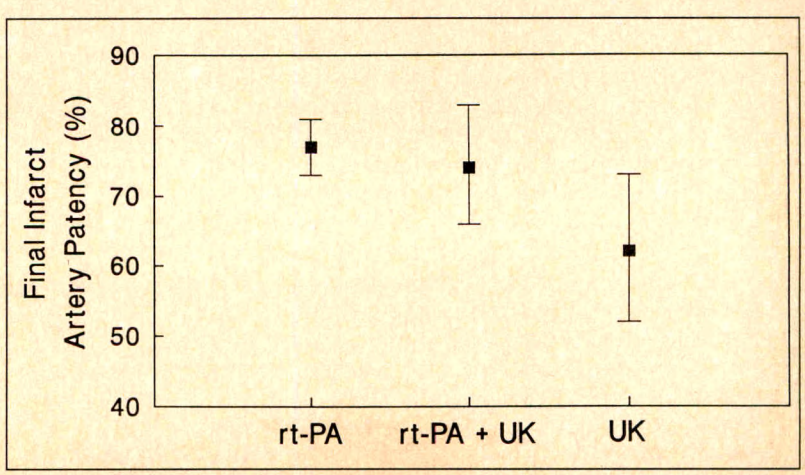


FIGURE 2. Median and 95% confidence limits for infarct artery patency for patients treated with tissue plasminogen activator (rt-PA), urokinase (UK) and combination therapy.

approach to managing recurrent ischemia could further explain our lower rate of reocclusion. Perhaps reocclusion was prevented by rapid intervention when recurrent ischemia occurred.

Patients in this study had worse left ventricular function both in terms of global ejection fraction as well as regional infarct zone function compared with most previous trials, possibly due to the high rate (53%) of multivessel disease. The lack of improvement in left ventricular function during the course of the hospitalization was similar to that of the Thrombolysis and Angioplasty in Myocardial Infarction-1 and -2 studies as well as the Thrombolysis in Myocardial Infarction trials.[5,7,10,21] Despite this expected finding, it was somewhat disappointing that patients who failed reperfusion and underwent rescue angioplasty did not improve their left ventricular function as seen in patients with combination therapy and rescue angioplasty in the Thrombolysis and Angioplasty in Myocardial Infarction-2 trial.[10,27]

Bleeding complications were substantial overall but were not significantly different compared with previous studies. Despite a marked increase in fibrin and fibrinogen degradation products and the sustained depletion of fibrinogen, the bleeding complications were comparable to reports of patients treated with recombinant tissue plasminogen activator monotherapy in the Thrombolysis and Angioplasty in Myocardial Infarction and Thrombolysis in Myocardial Infarction trials.[5,7,10,25,28] Most of the significant bleeding episodes occurred at periaccess sites and 1 patient (1%) experienced an intracranial bleed. Large-scale trials will be needed to determine the actual intracranial bleeding rate. The high percentage of patients receiving transfusions can be attributed to the frequent use of coronary artery bypass grafting in this study, as well as to our policy of liberal transfusion use; patients routinely underwent transfusion when the hematocrit approached 30. Since this trial, our threshold for transfusion in the hemodynamically stable patient has decreased to a hematocrit of 24.

The success rates with acute angioplasty were high, especially in the group with totally occluded arteries at the time of acute catheterization. This high technical success rate is similar to the 94% rate reported by Stack et al[20,29] when streptokinase was used as the thrombolytic agent. The results contrast with the results in the Thrombolysis and Angioplasty in Myocardial Infarction-1 and -3, European Cooperative Study Group and Thrombolysis in Myocardial Infarction trials with recombinant tissue plasminogen activator used as monotherapy, and emphasize the fact that a systemic lytic environment may be a healthy one for this "rescue" procedure.[5,7,22,25] The failure of 3 of 10 angioplasty procedures when the vessel was patent before acute angioplasty further confirms previous data supporting deferred angioplasty in this subgroup of patients.[5,30] Because these findings have now been confirmed in several studies, it is currently our practice to defer angioplasty if the infarct-related vessel is patent and the patient is asymptomatic and hemodynamically stable.

Several limitations of this study should be noted. The first is the absence of a control group or a concurrent comparison group. Second, patients were predominantly from a rural community setting and had more severe coronary disease on entry into this study compared with previous thrombolytic therapy trials. Because of more severe coronary disease and left ventricular dysfunction, patients were in general treated more aggressively after thrombolysis than is our usual strategy. Hence, their overall clinical outcomes are difficult to compare with previous less aggressive studies. Finally, our aggressive policy of early blood transfusion makes it difficult to accurately compare bleeding complications with other agents.

Acknowledgment: We are deeply grateful for the excellent secretarial and technical support provided by Cindy Day. We also appreciate the assistance of Daniel Mark, MD, MPH, and Paul Bunnell for manuscript review.

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APPENDIX
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Echocardiographic Evaluation of Segmental Wall Motion Early and Late After Thrombolytic Therapy in Acute Myocardial Infarction: The Western Washington Tissue Plasminogen Activator Emergency Room Trial

Catherine M. Otto, MD, John R. Stratton, MD, Charles Maynard, PhD, Ralph Althouse, MD, Karl-Arne Johannessen, MD, and J. Ward Kennedy, MD*

In 92 acute myocardial infarction (AMI) patients treated with tissue plasminogen activator 2.3 ± 1.2 hours after the onset of chest pain, echocardiography was performed at 11 ± 14 hours (early) and, in 49 patients, again at 13 ± 7 weeks (late). Infarct location and the left ventricular wall motion score index—the average score (normal = 1, hypokinetic = 2, akinetic = 3, dyskinetic = 4) for 20 segments—were determined by 2 observers unaware of clinical, angiographic or electrocardiographic data. Concordance between noninvasive infarct location by electrocardiography or echocardiography and infarct-related artery at angiography 4 ± 2 days later (n = 85) was 76 and 81%, respectively. The early wall motion score index was worse for anterior (1.8 ± 0.4) versus inferior (1.3 ± 0.2, p <0.0001) or posterior-lateral (1.6 ± 0.2, p = 0.0003) infarcts. Overall, the wall motion score index improved from early to late echocardiography (n = 49, 1.5 ± 0.3 to 1.3 ± 0.3, p = 0.0008). However, improvement was confined to those with time to treatment ≤2 hours (n = 22, 1.4 ± 0.3 to 1.2 ± 0.2, p <0.0001), and evidence of reperfusion at angiography (n = 38, 1.5 ± 0.3 to 1.2 ± 0.3, p <0.0001). The decrease in the wall motion score index was related to a decrease in the number of adjacent involved segments (5.5 ± 3.0 to 3.7 ± 3.9/patient, p = 0.0006). Thus, echocardiography early after AMI identifies infarct location. Improvement in regional wall motion is seen after early treatment with intravenous tissue plasminogen activator.

(Am J Cardiol 1990;65:132–138)

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Intravenous thrombolytic therapy in acute myocardial infarction (AMI) has been shown to result in decreased infarct size and an improvement in global and regional left ventricular systolic function at follow-up[1–10] as assessed by radionuclide and angiographic techniques. Two-dimensional echocardiography can be used to define the acute decrease in wall motion that occurs in AMI[11–15] and can provide useful information regarding infarct size,[16–18] anatomic location, complications and overall prognosis after AMI. Compared with other imaging modalities, echocardiography has 2 advantages: it is noninvasive and can be performed repeatedly and rapidly at the bedside. This study uses echocardiographic evaluation of left ventricular segmental wall motion in a community-based series of AMI patients receiving intravenous tissue plasminogen activator within 6 hours of the onset of chest pain to assess the utility of early echocardiography in identifying infarct location and severity; follow serial changes in regional wall motion in individual patients early and late after thrombolytic therapy; and determine whether time to treatment influenced early or late regional wall motion.

METHODS

Study protocol: The Western Washington Tissue Plasminogen Activator Emergency Room Trial enrolled 160 patients between January 18, 1987, and January 13, 1988. The overall results of this trial have been reported elsewhere.[19] Patients were <76 years of age, with symptoms typical of AMI within 6 hours of presentation *and* with an electrocardiogram showing ST-segment elevation >0.10 mV or tall peaked "hyperacute" T waves in ≥2 associated leads. The electrocardiogram was reviewed by an observer unaware of clinical data for infarct location, defined as anterior (I, aVL, V_1 to V_6), inferior (II, III, aVF) or posterior (aVR and V_1 to V_2). Patients were excluded for any contraindication to thrombolysis or systemic anticoagulation, a major surgical procedure or trauma within the previous 2 months, recent cardiopulmonary resuscitation, cerebrovascular disease or concomitant known disease likely to limit lifespan to <6 months in the absence of AMI.

After informed consent, treatment with tissue plasminogen activator was begun (time from onset of pain = 141 ± 69 minutes) with a 6-mg bolus, followed by 54

TABLE I Selected Clinical Characteristics

	Early Echo (n = 92)	tPA Patients with Paired Early and Late Echo (n = 49)	tPA Patients Without Early Echo (n = 68)
History			
Age (yrs)	58 ± 11	58 ± 10	58 ± 8
Male sex (%)	71 (77)	40 (82)	59 (87)
Prior MI (%)	14 (15)	7 (14)	12 (18)
Angina (%)	35 (38)	18 (37)	24 (35)
Clinical (%)			
Hypotensive	8 (9)	5 (10)	6 (9)
Shock	2 (2)	2 (4)	2 (3)
Pulmonary edema	6 (7)	5 (10)	2 (3)
Cardioversion	4 (4)	1 (2)	2 (3)
CPR	2 (2)	1 (2)	2 (3)
Time to tPA (min)	138 ± 69	138 ± 60	144 ± 70
Laboratory			
Peak CPK (IU)	1,885 ± 1,653	2,028 ± 1,611	2,048 ± 1,811
Time to peak CPK (hrs)	14.5 ± 15.5	13.8 ± 5.5	16.5 ± 16.7
Procedures (%)			
Cardiac catheterization	85 (92)	48 (98)	62 (91)
PTCA	16 (17)	10 (20)	16 (24)
CABG	16 (17)	8 (16)	20 (29)
Hospital death (%)	4 (4)	0 (0)	5 (7)

p >0.05 for all comparisons of early echo versus those without.
CABG = coronary artery bypass grafting; CPK = creatinine phosphokinase; CPR = cardiopulmonary resuscitation; Echo = echocardiography; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; tPA = tissue plasminogen activator.

mg in the first hour and 10 mg/hr for 4 more hours (total dose 100 mg). The initial 10 patients received a total dose of 150 mg. Systemic anticoagulation with heparin was maintained for 96 hours, followed by aspirin 325 mg daily. Total creatinine phosphokinase was determined (normal range 1 to 100 U/liter) every 4 hours for the first 24 hours.

Echocardiography was performed early after therapy in 100 of 160 patients (62.5%). Of these 100 patients, coronary angiography and left ventricular angiography were performed in 85 patients 4 ± 2 days after treatment. The angiogram was reviewed by a reading committee to determine the infarct-related artery (left anterior descending, posterior descending or circumflex artery), and the extent of reperfusion using the Thrombolysis in Myocardial Infarction trial (TIMI) criteria.[20] One to 4 months after hospitalization, 49 of these patients returned for repeat 2-dimensional echocardiography, radionuclide ventriculography and thallium infarct size determination.[21] Other forms of reperfusion before late echocardiography included percutaneous transluminal coronary angioplasty in 10 and coronary artery bypass grafting in 8 of these 49 patients.

Echocardiography: A technically adequate echocardiogram was performed at a mean ± 1 standard deviation of 11 ± 14 hours (early) after the onset of chest pain in 92 patients with 85 of 92 (92%) performed within 24 hours of the onset of chest pain. Early echocardiography was technically inadequate in 8 patients (8%). Of the 92 adequate echocardiograms, the technical quality was excellent in 12 (13%), good in 44 (48%) and fair in 36 (39%) patients. Most (85%) of the early echocardiograms were performed at 4 of the 7 participating hospitals and included 83% of the total population at these 4 hospitals.

Echocardiography was repeated at 13 ± 7 weeks (late) in 49 of these patients. Technical quality for endocardial definition and wall motion was excellent in 20 (41%), good in 20 (41%) and fair in 9 (18%) patients. There were no significant differences in any clinical characteristics between the study patients who did and who did not undergo echocardiography or between those with paired early and late studies and the entire group (Table I).

Two-dimensional images of the left ventricle were recorded on videotape in parasternal long- and short-axis views, and in apical 4-chamber, 2-chamber and long-axis views. The echocardiograms were interpreted by consensus of 2 obervers blinded to clinical, electrocardiographic and angiographic data and (for the late study) unaware of the interpretation of the early echocardiographic study. For each of 20 left ventricular segments,[22,23] wall motion was graded as: normal = 1, hypokinetic = 2, akinetic = 3 and dyskinetic = 4. Nonvisualized segments (1.1% of total) were eliminated from further analysis. The wall motion score index was calculated as the sum of the grades for each segment divided by the number of segments. Infarct location was defined by echocardiography based on the pattern of the wall motion abnormality as shown in Figure 1.

Interpretation reproducibility was assessed in a randomly selected subset of early and late echocardiograms (18). On a segment-by-segment basis, there was complete agreement between the 2 readings for 305 of 376 segments (81%), with disagreement by >1 grade for only 7 (2% of total) segments. The wall motion score index also agreed closely (1.3 ± 0.3 vs 1.3 ± 0.3, difference not significant).

Statistical methods: Infarct locations by electrocardiography and echocardiography were compared with

angiographic infarct-related artery by chi-square test. The unpaired t test was used to compare subgroups for the early wall motion score index. The paired t test was used to examine early and late differences for the patients with both studies with respect to the wall motion score index and number of involved segments. Linear regression and correlation were used to compare the wall motion score index with infarct size, radionuclide and angiographic ejection fractions.

RESULTS

Infarct location by early echocardiography: A specific infarct location could be determined by 2-dimensional echocardiography in 83 of the 92 adequate early

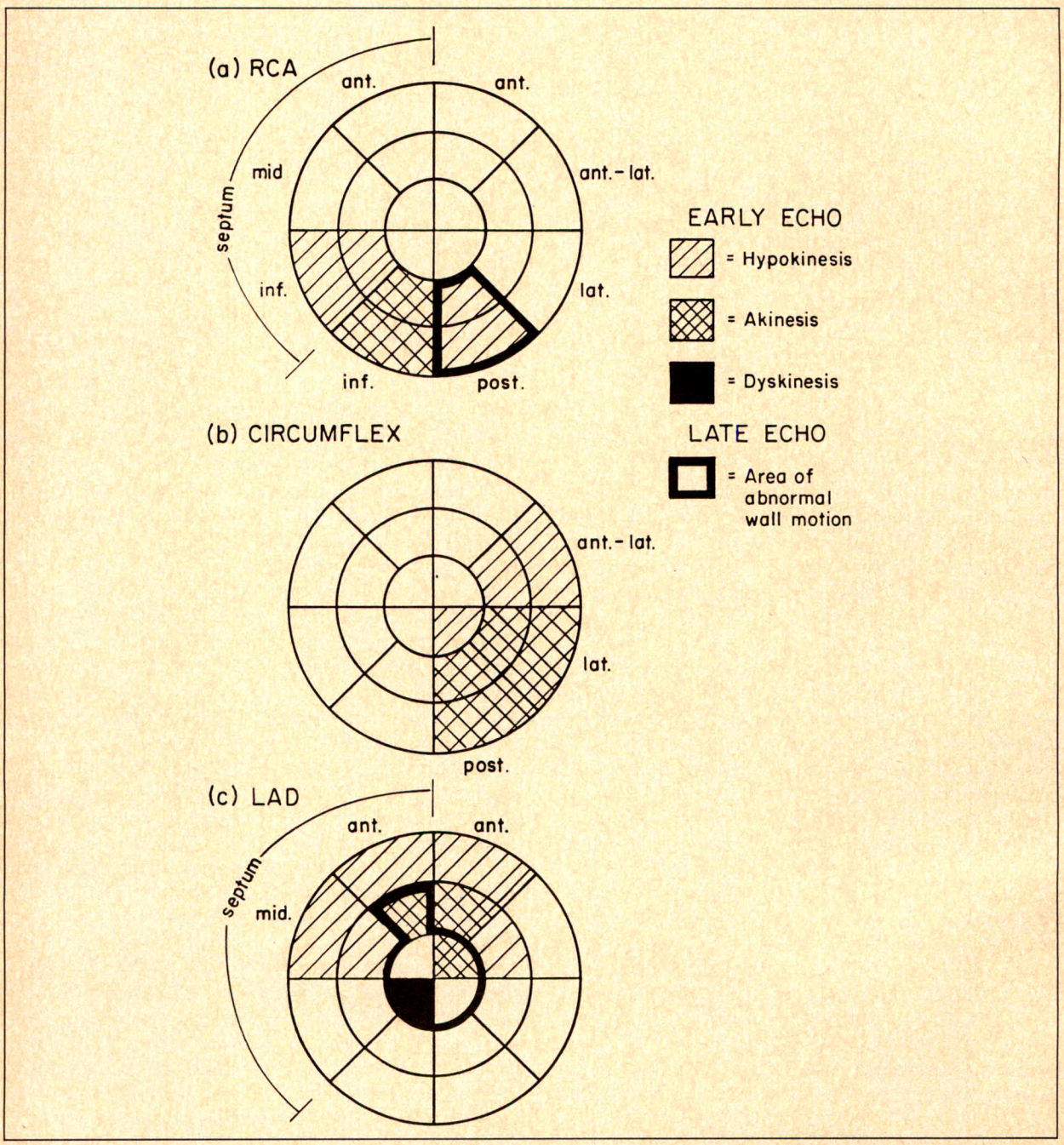


FIGURE 1. Target diagram of the left ventricle.[23] The ventricle, shown as if viewed from the apex, is divided into 3 regions—basal (outer ring), mid- and apical (in center). There are 8 segments each at basal and mid-ventricular levels and 4 apical segments. The pattern of abnormal wall motion is illustrated for 3 cases with the acute study on the *left* and the late study on the *right*. *A*, Case 3011: Inferior infarct by echocardiography with the right coronary identified as the infarct-related artery at subsequent angiography. The wall motion score index improved from 1.4 to 1.2, with 1 segment hypokinetic and 1 segment akinetic at late echocardiography. *B*, Case 2008: Posterolateral infarct by echocardiography, circumflex artery at angiography, wall motion score index 1.6 early and 1.0 (entirely normal) at follow-up. *C*, Case 1016: Anterior infarct by echocardiography, left anterior descending artery at angiography. The wall motion score index improved from 1.7 to 1.2, with all involved segments hypokinetic at late echocardiography. Ant = anterior; inf = inferior; ECHO = echocardiogram; lat = lateral; post = posterior; RCA = right coronary artery.

echocardiograms: anterior in 29, inferior in 40 and posterior-lateral in 14 patients. Six early echocardiograms showed no wall motion abnormality, whereas in 3 a wall motion abnormality was identified but infarct location was ambiguous (apical in 2, basal in 1).

Of the 75 patients with known echocardiographic infarct location and subsequent angiography, concordance for infarct locations was 81%, compared to 76% for the 82 patients with infarct location by electrocardiography and angiography (Figure 2). Concordance between echocardiographic and electrocardiographic infarct location was 74% ($p < 0.0001$).

Early segmental wall motion: The early wall motion score index was higher (more abnormal wall motion) for echocardiographically defined anterior ($n = 29$, 1.8 ± 0.4) or posterior-lateral ($n = 14$, 1.6 ± 0.2) than for inferior ($n = 40$, 1.3 ± 0.2) infarcts ($p < 0.0001$ and $p = 0.0003$ by unpaired t test, respectively, Figure 3). These differences also were significant by analysis of variance ($p < 0.0001$).

The entire study population was divided into 2 equal groups based on time from onset of symptoms to treatment (≤2 hours and >2 hours). There was no relation between the early wall motion score index and time to treatment (≤2 hours, $n = 48$, 1.5 ± 0.4 vs >2 hours, $n = 44$, 1.5 ± 0.3, difference not significant), or TIMI reperfusion grade (grade 0, $n = 18$, 1.5 ± 0.2 vs TIMI grade ≥1, $n = 67$, 1.4 ± 0.3, $p = 0.19$). There was a statistically significant relation between the early wall motion score index and time to peak creatinine phosphokinase (≤12 hours, $n = 31$, 1.6 ± 0.4 vs >12 hours, $n = 61$, 1.4 ± 0.3, $p = 0.013$).

Comparison of early and late segmental wall motion: In the 49 patients with both early (11 ± 14 hours) and late (13 ± 7 weeks) echocardiography, the wall motion score index improved in 37 patients, was unchanged in 5 (initially normal in 4) patients and worsened in 7 patients. The mean wall motion score index improved significantly (1.5 ± 0.3 to 1.3 ± 0.3, $p = 0.0008$). This improvement was significant statistically both in the subgroup with intervening coronary angioplasty or bypass grafting (1.5 ± 0.3 to 1.3 ± 0.3, $p = 0.05$) and those with no intervening procedure (1.4 ± 0.3 to 1.3 ± 0.3, $p = 0.002$).

The improvement in segmental wall motion (Figure 4) was confined to those patients with thrombolytic treatment ≤2 hours after onset of symptoms ($n = 22$, 1.4 ± 0.3 to 1.2 ± 0.2, $p < 0.0001$) compared to those with treatment >2 hours ($n = 27$, 1.5 ± 0.3 to 1.4 ± 0.4, $p = 0.23$) and those with TIMI grade ≥1 at angiography ($n = 38$, 1.5 ± 0.3 to 1.2 ± 0.3, $p < 0.0001$) compared to those with TIMI grade 0 ($n = 9$, 1.5 ± 0.2 to 1.5 ± 0.4, difference not significant). In the 22 patients treated ≤2 hours, those with angiographic evidence of reperfusion ($n = 19$, 1.4 ± 0.3 to 1.2 ± 0.2, $p < 0.0001$) showed improvement whereas the few without reperfusion did not ($n = 3$, 1.5 ± 0.1 to 1.4 ± 0.2, difference not significant).

The wall motion score index improved most in those with anterior infarcts ($n = 13$, 1.7 ± 0.3 to 1.4 ± 0.4, $p = 0.048$) and posterior-lateral infarcts ($n = 13$, 1.5 ± 0.3 to 1.2 ± 0.2, $p = 0.002$) compared to inferior infarcts ($n = 21$, 1.3 ± 0.3 to 1.2 ± 0.3, difference not significant) as defined by angiographic infarct-related artery.

The improvement in the wall motion score index was related to a decrease in the number of segments with abnormal wall motion per patient (mean number of abnormal segments early: 5.5 ± 3.0; late: 3.7 ± 3.9, $p = 0.0006$) (Figure 5). The average wall motion score for *only* the abnormal segments did not change (2.5 ± 0.4 to 2.5 ± 0.4, difference not significant). Of the 149 segments that showed return of normal wall motion between the early and late echocardiograms, 127 (85.2%) were in segments at the edge of the initial region of abnormal wall motion. In 20 patients (41%), wall motion was entirely normal at late echocardiography. Examples of the improvement in wall motion are shown in Figure 1.

The late wall motion score index showed a significant linear correlation with angiographic ejection fraction done at 4 ± 2 days after infarction ($r = -0.50$, $p = 0.0013$), thallium infarct size at 13 ± 7 weeks ($r = 0.65$, $p < 0.0001$) and radionuclide ejection fraction at 13 ± 7 weeks ($r = -0.66$, $p < 0.0001$) but there was wide scatter of the data for these relations.

DISCUSSION

In this community-based series of AMI patients, we used echocardiographic imaging for assessment of regional left ventricular systolic function early and again late after AMI.

Early echocardiography: Although early echocardiography was performed after initiation of thrombolytic therapy, a segmental wall motion abnormality consis-

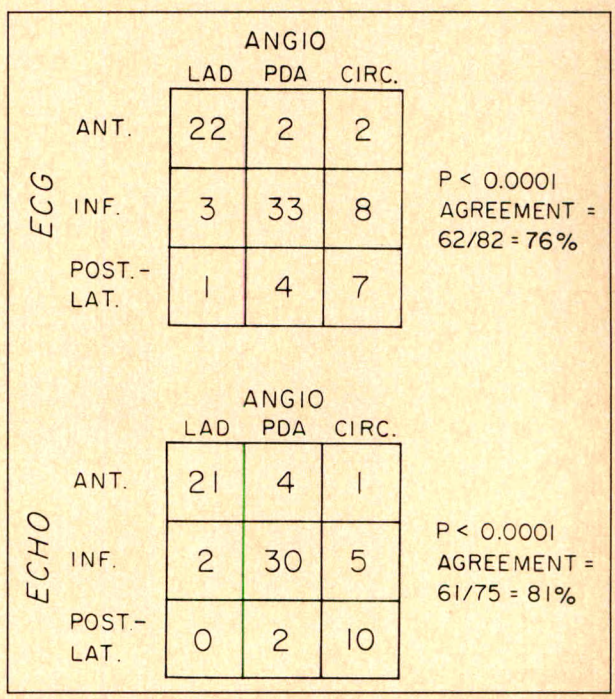


FIGURE 2. Infarct location by electrocardiography (ECG) (*top*) and by echocardiography (*bottom*) versus angiographic infarct-related artery. Angio = coronary angiography; Circ = circumflex artery; PDA = posterior descending artery.

tent with AMI was present in nearly all patients. All 6 patients with normal wall motion on early echocardiography had reperfusion and were alive at 1 year of follow-up. Whereas the area-at-risk may have been underestimated due to reperfusion before echocardiographic imaging, myocardial "stunning" [24,25] should minimize this underestimate. Conversely, the tethering effect of adjacent segments can result in overestimation of infarct size by echocardiography.[11,17,18]

Our findings are in agreement with prior studies that have demonstrated that anatomic infarct location and the extent of regional ventricular dysfunction can be identified with echocardiography.[9,11–17,26] Discordance between echocardiographic infarct location and the infarct-related artery at subsequent angiography most likely relates to variability in coronary anatomy because discordance typically occurred with septal and inferior-posterior wall motion abnormalities. In addition, although angiography performed during the acute phase of AMI provides reliable identification of the infarct artery,[27] late angiography is less reliable, especially in multivessel disease.

Late echocardiography: The extent of wall motion abnormality late after AMI correlates with other measures of infarct size and left ventricular function.[16] Comparison of paired early and late echocardiograms demonstrates that patients with reperfusion have significant improvement in regional left ventricular systolic function.[9,28,29] In this study the improvement in regional ventricular function was due to a decrease in the number of abnormal segments and was most marked in those treated within 2 hours of the onset of symptoms.

Study limitations: Comparison of echocardiographic regional wall motion between the entire group of pa-

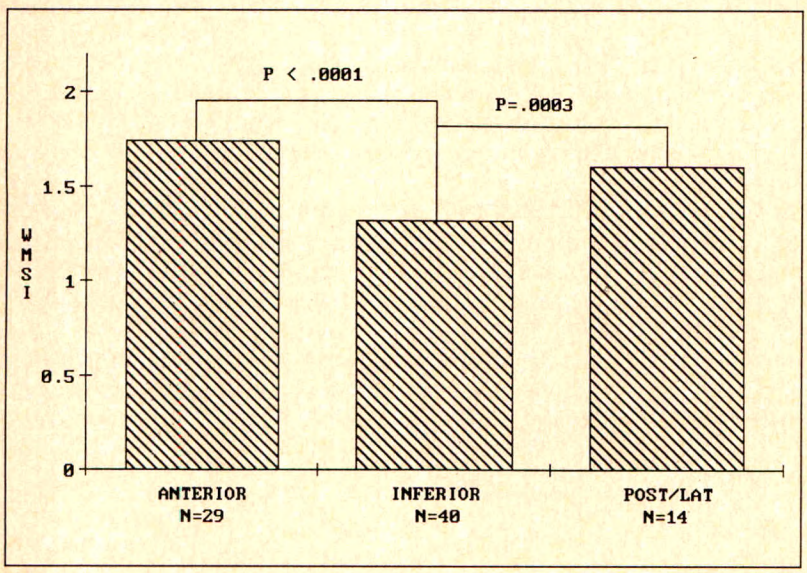


FIGURE 3. Wall motion score index (WMSI) at early echocardiography versus infarct location (by echocardiography).

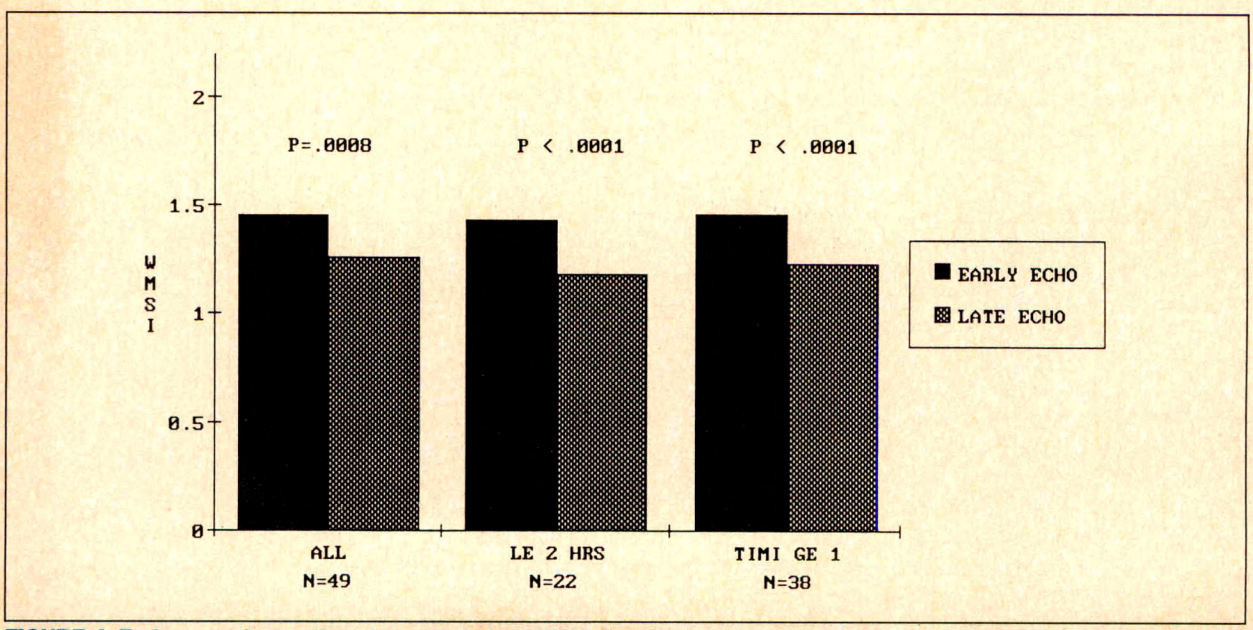


FIGURE 4. Early versus late wall motion score index (WMSI) for all patients and for subgroups with treatment ≤2 hours (LE 2 hrs) and Thrombolysis in Myocardial Infarction reperfusion grade ≥1 (TIMI GE 1).

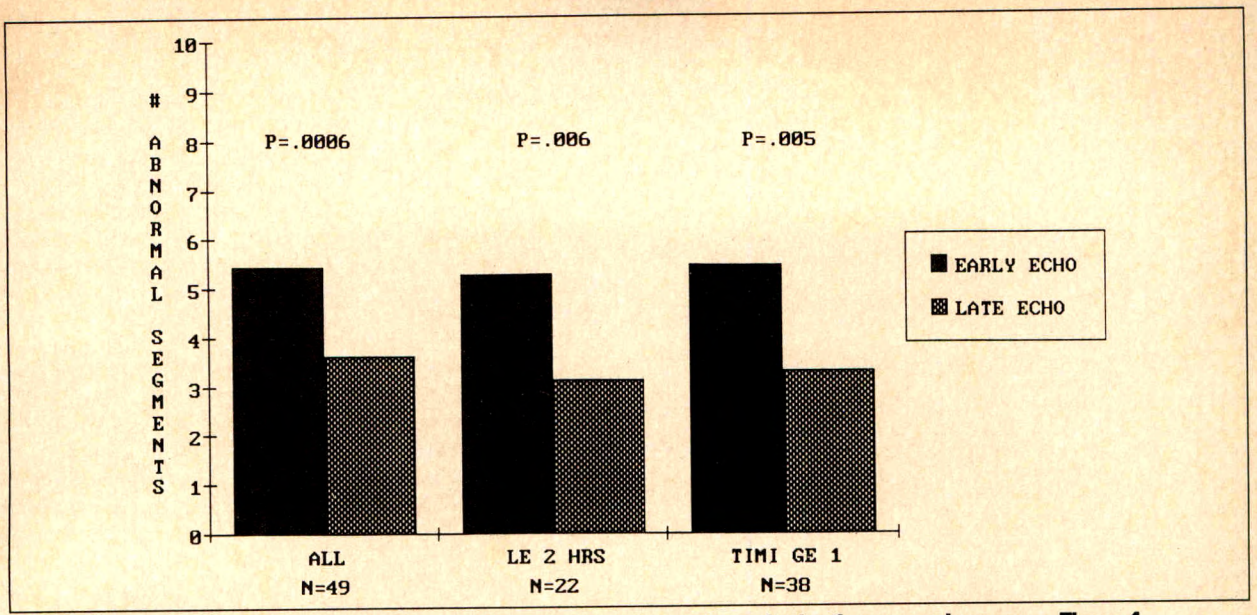


FIGURE 5. Number of abnormal segments at early versus late echocardiography for the same subgroups as Figure 4. Abbreviations as in Figure 4.

tients receiving thrombolytic therapy and a control group of untreated AMI patients was considered unethical given the known benefits of thrombolytic therapy.[1-10] Wall motion was assessed qualitatively because accurate tracing of the endocardial borders for quantitative analysis would have been possible in only a relatively small subset. In addition, the time course of recovery of wall motion cannot be assessed because only 2 sets of echocardiograms were performed.[29,30]

Clinical implications: Echocardiography early after thrombolytic therapy in patients with AMI provides useful information on infarct location and the area of myocardium at risk. Improvement in regional wall motion, due to a decrease in the number of abnormal segments, occurs in patients with reperfusion treated with tissue plasminogen activator <2 hours after the onset of symptoms.

Acknowledgment: The assistance of Michelle Olsufka, RN, in data collection, and Sharon Kemp in manuscript preparation is acknowledged.

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APPENDIX

Participants: The cardiologists participating in the Echocardiography Substudy of the Western Washington Tissue Plasminogen Activator Emergency Room Trial were: James K. Fritz, MD (*Group Health Central, Seattle*), Douglas Weaver, MD, and Leonard Cobb, MD (*Harborview Medical Center, Seattle*), Arthur Lee, MD (*Harrison Memorial, Bremerton*), John A. Murray, MD (*Northwest Hospital, Seattle*), J. Ward Kennedy, MD, and Ralph Althouse, MD (*University Hospital, Seattle*), James L. Ritchie, MD (*Veterans Administration Medical Center, Seattle*) and Ted Steudal,MD (*Madigan Army Hospital, Fort Lewis*).

The sonographers who skillfully performed the echocardiograms were: Miles Matsuda, RDMS, and Chris Hixson, RDMS (*Veterans Administration Medical Center, Seattle*); Eric Sisk, RDMS (*Harborview Medical Center, Seattle*); Jeff Pope, RDMS, Darcee Dahl, RDMS, Patty Jackson, RDMS and Cory Sutherland, RDMS (*Northwest Hospital, Seattle*); Cindy Cronin, RDMS (*Group Health Central, Seattle*); Blanche Hattendorf, RDMS, and Jana Olson, RDMS (*Harrison Memorial, Bremerton*); Carolyn Gardner, RDMS, Carol Kraft, RDMS, and Michelle Fujioka, RDMS (*University Hospital, Seattle*).

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NONIONIC CONTRAST MEDIA:

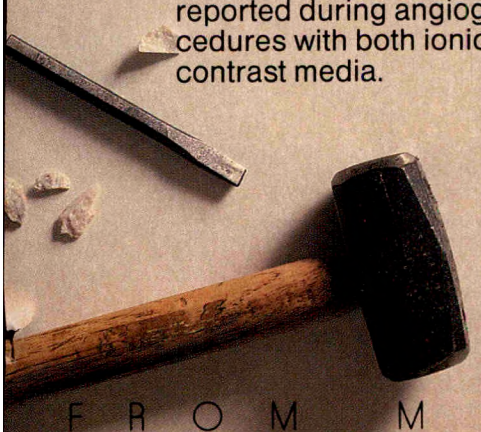
Nonionic iodinated contrast media inhibit blood coagulation, in vitro, less than ionic contrast media. Clotting has been reported when blood remains in contact with syringes containing nonionic contrast media.

IONIC CONTRAST MEDIA:

Ionic iodinated contrast media inhibit blood coagulation, in vitro, more than nonionic contrast media. Nonetheless, it is prudent to avoid prolonged contact of blood with syringes containing ionic contrast media.*

Comparative studies demonstrate that nonionic media have a weaker inhibitory effect on clotting in vitro than ionic media.[1-4] The new labeling changes recently required for contrast media reflect this difference in anticoagulant properties between nonionic and ionic media.

When using any contrast agent, good angiographic technique is essential. However, even when meticulous technique is applied, some mixing of blood with contrast media in syringes and catheters is possible. Thromboembolic events have been reported during angiographic procedures with both ionic and nonionic contrast media.



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CONTRAINDICATIONS

HEXABRIX is contraindicated for use in myelography. Refer to PRECAUTIONS concerning hypersensitivity. Hysterosalpingography should not be performed during the menstrual period; in pregnant patients; in patients with known infection in any portion of the genital tract; or in patients in whom cervical conization or curettage has been performed within 30 days. Arthrography should not be performed if infection is present in or near the joint.

WARNINGS

Ionic iodinated contrast media inhibit blood coagulation, *in vitro*, more than nonionic contrast media. Nonetheless, it is prudent to avoid prolonged contact of blood with syringes containing ionic contrast media.

Serious, rarely fatal, thromboembolic events causing myocardial infarction and stroke have been reported during angiographic procedures with both ionic and nonionic contrast media. Therefore, meticulous intravascular administration technique is necessary, particularly during angiographic procedures, to minimize thromboembolic events. Numerous factors, including length of procedure, catheter and syringe material, underlying disease state, and concomitant medications may contribute to the development of thromboembolic events. For these reasons, meticulous angiographic techniques are recommended including close attention to guidewire and catheter manipulation, use of manifold systems and/or three-way stopcocks, frequent catheter flushing with heparinized saline solutions and minimizing the length of the procedure. The use of plastic syringes in place of glass syringes has been reported to decrease but not eliminate the likelihood of *in vitro* clotting.

As with any contrast medium, serious neurologic sequelae, including permanent paralysis, can occur following cerebral arteriography, selective spinal arteriography and arteriography of vessels supplying the spinal cord. The injection of a contrast medium should never be made following the administration of vasopressors, since they strongly potentiate neurologic effects.

In patients with subarachnoid hemorrhage, a rare association between contrast administration and clinical deterioration, including convulsions and death, has been reported. Therefore, administration of intravascular iodinated contrast media in these patients should be undertaken with caution.

A definite risk exists in the use of intravascular contrast agents in patients who are known to have multiple myeloma. In such instances anuria has developed, resulting in progressive uremia, renal failure and eventually death. Although neither the contrast agent nor dehydration has separately proved to be the cause of anuria in myeloma, it has been speculated that the combination of both may be a causative factor. The risk in myelomatous patients is not a contraindication to the procedure; however, partial dehydration in the preparation of these patients for the examination is not recommended since this may predispose to precipitation of myeloma protein in the renal tubules. No form of therapy, including dialysis, has been successful in reversing the effect. Myeloma, which occurs most commonly in persons over 40, should be considered before instituting intravascular administration of contrast agents.

Administration of radiopaque materials to patients known or suspected to have pheochromocytoma should be performed with extreme caution. If, in the opinion of the physician, the possible benefits of such procedures outweigh the considered risks, the procedures may be performed; however, the amount of radiopaque medium injected should be kept to an absolute minimum. The blood pressure should be assessed throughout the procedure, and measures for treatment of a hypertensive crisis should be available.

Since intravascular administration of contrast media may promote sickling in individuals who are homozygous for sickle cell disease, fluid restriction is not advised.

In patients with advanced renal disease, iodinated contrast media should be used with caution and only when the need for the examination dictates, since excretion of the medium may be impaired. Patients with combined renal and hepatic disease, those with severe hypertension or congestive heart failure and recent renal transplant recipients present an additional risk.

Renal failure has been reported in patients with liver dysfunction who were given an oral cholecystographic agent followed by an intravascular iodinated radiopaque agent and also in patients with occult renal disease, notably diabetics and hypertensives. In these classes of patients there should be no fluid restriction and every attempt made to maintain normal hydration prior to contrast medium injection, since dehydration is the single most important factor influencing further renal impairment.

Caution should be exercised in performing contrast medium studies in patients with endotoxemia and/or those with elevated body temperatures.

Reports of thyroid storm occurring following the intravascular use of iodinated radiopaque agents in patients with hyperthyroidism or with an autonomously functioning thyroid nodule, suggest that this additional risk be evaluated before use of this drug. Iodine-containing contrast agents may alter the results of thyroid function tests which depend on iodine estimation, e.g., PBI, and may also affect results of radioactive iodine uptake studies. Such tests, if indicated, should be performed prior to the administration of this preparation.

PRECAUTIONS

Diagnostic procedures which involve the use of iodinated intravascular contrast agents should be carried out under the direction of personnel skilled and experienced in the particular procedure to be performed. All procedures utilizing contrast media carry a definite risk of producing adverse reactions. While most reactions are minor, life-threatening and fatal reactions may occur without warning, and this risk must be weighed against the benefit of the procedure. A fully equipped emergency cart, or equivalent supplies and equipment, and personnel competent in recognizing and treating adverse reactions of all types should always be available. If a serious reaction should occur, immediately discontinue administration. Since severe delayed reactions have been known to occur, emergency facilities and competent personnel should be available for at least 30 to 60 minutes after administration. (See ADVERSE REACTIONS.)

Preparatory dehydration is dangerous and may contribute to acute renal failure in infants, young children, the elderly, patients with pre-existing renal insufficiency, patients with multiple myeloma, patients with advanced vascular disease and diabetic patients.

Acute renal failure has been reported in diabetic patients with diabetic nephropathy and in susceptible non-diabetic patients (often elderly with pre-existing renal disease) following the administration of iodinated contrast agents. Therefore, careful consideration of the potential risks should be given before performing this radiographic procedure in these patients.

Severe reactions to contrast media often resemble allergic responses. This has prompted the use of several provocative pretesting methods, none of which can be relied on to predict severe reactions. No conclusive relationship between severe reactions and antigen-antibody reactions or other manifestations of allergy has been established. The possibility of an idiosyncratic reaction in patients who have previously received a contrast medium without ill effect should always be considered. Prior to the injection of any contrast medium, the patient should be questioned to obtain a medical history with emphasis on allergy and hypersensitivity. A positive history of bronchial asthma or allergy (including food), a family history of allergy, or a previous reaction or hypersensitivity to a contrast agent may imply a greater than usual risk. Such a history may be more accurate than pre-testing in predicting the potential for reaction, although not necessarily the severity or type of reaction in the individual case. A positive history of this type does not arbitrarily contraindicate the use of a contrast agent when a diagnostic procedure is thought essential, but does call for caution. (See ADVERSE REACTIONS.)

Prophylactic therapy including corticosteroids and antihistamines should be considered for patients who present with a strong allergic history, a previous reaction to a contrast medium, or a positive pre-test since in these patients the incidence of reaction is two to three times that of the general population. Adequate doses of corticosteroids should be started early enough prior to contrast medium injection to be effective and should continue through the time of injection and for 24 hours after injection. Antihistamines should be administered within 30 minutes of the contrast medium injection. Recent reports indicate that such pre-treatment does not prevent serious life-threatening reactions, but may reduce both their incidence and severity. A separate syringe should be used for these injections.

General anesthesia may be indicated in the performance of some procedures in selected patients; however, a higher incidence of adverse reactions has been reported in these patients, and may be attributable to the inability of the patient to identify untoward symptoms or to the hypotensive effect of anesthesia which can prolong the circulation time and increase the duration of contact of the contrast agent.

Angiography should be avoided whenever possible in patients with homocystinuria because of the risk of inducing thrombosis and embolism.

PRECAUTIONS FOR SPECIFIC PROCEDURES

Pediatric Angiocardiography: It is advisable to monitor for ECG and vital signs changes throughout the procedure.

When large individual doses are administered, sufficient time should be allowed for any observed changes to return to or near baseline prior to making the next injection.

Caution should be used when making right heart injections in patients with pulmonary hypertension or incipient heart failure, since this may lead to increased right side pressures with subsequent bradycardia and systemic hypotension. Patients with pulmonary disease present additional risks.

Caution is advised in cyanotic infants since apnea, bradycardia, other arrhythmias and a tendency to acidosis are more likely to occur.

Since infants are more likely to respond with convulsions than are adults, the amount of total dosage is of particular importance. Repeated injections are hazardous in infants weighing less than 7 kg, particularly when these infants have pre-existing compromised right heart function or obliterated pulmonary vascular beds.

Selective Coronary Arteriography with or without left ventriculography: During the administration of large doses of HEXABRIX, continuous monitoring of vital signs is desirable. Caution is advised in the administration of large volumes to patients with incipient heart failure because of the possibility of aggravating the pre-existing condition. Hypotension should be corrected promptly since it may result in serious arrhythmias.

Special care regarding dosage should be observed in patients with right ventricular failure, pulmonary hypertension, or stenotic pulmonary vascular beds because of hemodynamic changes which may occur after injection into the right heart outflow tract.

Peripheral Arteriography: Moderate decreases in blood pressure occur frequently with intra-arterial (brachial) injections. This change is usually transient and requires no treatment; however, the blood pressure should be monitored for approximately ten minutes following injection.

Extreme caution during injection of the contrast agent is necessary to avoid extravasation and fluoroscopy is recommended. This is especially important in patients with severe arterial disease.

Cerebral Angiography: Cerebral angiography should be performed with special caution in patients with advanced arteriosclerosis, severe hypertension, cardiac decompensation, senility, recent cerebral thrombosis or embolism, and migraine.

Intra-Arterial Digital Subtraction Angiography: The risks associated with IA-DSA are those usually attendant with catheter procedures. Following the procedure, gentle pressure hemostasis is required, followed by observation and immobilization of the limb for several hours to prevent hemorrhage from the site of arterial puncture.

Patient motion, including respiration and swallowing, can result in misregistration leading to image degradation and non-diagnostic studies.

Intravenous Digital Subtraction Angiography: The risks associated with IV-DSA include those usually attendant with catheter procedures and include intramural injections, vessel dissection and tissue extravasation. The potential risk is reduced when small test injections of contrast medium are made under fluoroscopic observation to insure that the catheter tip is properly positioned and, in the case of peripheral placement, that the vein is of adequate size.

Patient motion, including respiration and swallowing, can result in misregistration leading to image degradation and non-diagnostic studies.

Peripheral Venography: Special care is required when venography is performed in patients with suspected thrombosis, phlebitis, severe ischemic disease, local infection or a totally obstructed venous system.

Extreme caution during injection of contrast media is necessary to avoid extravasation and fluoroscopy is recommended. This is especially important in patients with severe arterial or venous disease.

Excretory Urography: Infants and small children should not have any fluid restrictions prior to excretory urography. (See WARNING and PRECAUTIONS concerning preparatory dehydration.)

Contrast Enhancement in Body Computed Tomography: Patient cooperation is essential since patient motion, including respiration, can markedly affect image quality. The use of an intravascular contrast medium can obscure tumors in patients undergoing CT evaluation of the liver, resulting in a false negative diagnosis. Dynamic CT scanning is the procedure of choice for malignant tumor enhancement.

Arthrography: Strict aseptic technique is required to prevent the introduction of infection. Fluoroscopic control should be used to insure proper introduction of the needle into the synovial space and prevent extracapsular injection. Aspiration of excessive synovial fluid will reduce the pain on injection and prevent the dilution of the contrast agent. It is important that undue pressure not be exerted during the injection.

Hysterosalpingography: Caution should be exercised in patients suspected of having cervical or tubal carcinoma to avoid possible spread of the lesion by the procedure. Delayed onset of pain and fever (1-2 days) may be indicative of pelvic infection.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term animal studies have been performed to evaluate carcinogenic potential. However, animal studies suggest that this drug is not mutagenic and does not affect fertility in males or females.

Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at doses up to two times the maximum adult human dose and have revealed no evidence of impaired fertility or harm to the fetus due to HEXABRIX. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Ioxaglate salts are excreted unchanged in human milk. Because of the potential for adverse effects in nursing infants, bottle feedings should be substituted for breast feedings for 24 hours following the administration of this drug.

Pediatric Use: Safety and effectiveness in children has been established in pediatric angiocardiography and intravenous excretory urography. Data have not been submitted to support the safety and effectiveness of HEXABRIX in any other indication.

(Precautions for specific procedures receive comment under that procedure.)

ADVERSE REACTIONS

Adverse reactions to injectable contrast media fall into two categories: chemotoxic reactions and idiosyncratic reactions.

Chemotoxic reactions result from the physiochemical properties of the contrast media, the dose and the speed of injection. All hemodynamic disturbances and injuries to organs or vessels perfused by the contrast medium are included in this category.

Idiosyncratic reactions include all other reactions. They occur more frequently in patients 20 to 40 years old. Idiosyncratic reactions may or may not be dependent on the dose injected, the speed of injection, the mode of injection and the radiographic procedure. Idiosyncratic reactions are subdivided into minor, intermediate and severe. The minor reactions are self-limited and of short duration; the severe reactions are life-threatening and treatment is urgent and mandatory.

NOTE: Not all of the following adverse reactions have been reported with HEXABRIX. Because HEXABRIX is an iodinated intravascular contrast agent, all of the side effects and toxicity associated with agents of this class are theoretically possible, and this should be borne in mind when HEXABRIX is administered.

Severe, life-threatening anaphylactoid reactions, mostly of cardiovascular origin, have occurred following the administration of HEXABRIX as well as other iodine-containing contrast agents. Most deaths occur during injection or 5 to 10 minutes later; the main feature being cardiac arrest with cardiovascular disease as the main aggravating factor. Isolated reports of hypotensive collapse and shock are found in the literature. Based upon clinical literature, reported deaths from the administration of conventional iodinated contrast agents range from 6.6 per 1 million (0.00066 percent) to 1 in 10,000 patients (0.01 percent).

Regardless of the contrast agent employed, the overall estimated incidence of serious adverse reactions is higher with coronary arteriography than with other procedures. Cardiac decompensation, serious arrhythmias, or myocardial ischemia or infarction may occur during coronary arteriography and left ventriculography.

The most frequent adverse reactions are nausea, vomiting, facial flush and a feeling of body warmth. These are usually of brief duration. In double-blind clinical trials, HEXABRIX produced less discomfort upon injection (pain and heat) when compared to various other contrast agents. Other reactions include the following:

Hypersensitivity reactions: Dermal manifestations of urticaria with or without pruritus, erythema and maculopapular rash. Dry mouth. Sweating. Conjunctival symptoms. Facial, peripheral and angioneurotic edema. Symptoms related to the respiratory system include sneezing, nasal stuffiness, coughing, choking, dyspnea, chest tightness and wheezing, which may be initial manifestations of more severe and infrequent reactions including asthmatic attack, laryngospasm and bronchospasm with or without edema, pulmonary edema, apnea and cyanosis. Rarely, these allergic-type reactions can progress into anaphylaxis with loss of consciousness, coma, severe cardiovascular disturbances, and death.

Cardiovascular reactions: Generalized vasodilation, flushing and venospasm. Occasionally thrombosis or, rarely, thrombophlebitis. Extremely rare cases of disseminated intravascular coagulation resulting in death have been reported. Severe cardiovascular responses include rare cases of hypotensive shock, coronary insufficiency, cardiac arrhythmia, fibrillation and arrest. These severe reactions are usually reversible with prompt and appropriate management; however, fatalities have occurred.

Technique reactions: Extravasation with burning pain, hematomas, ecchymosis and tissue necrosis, vascular constriction due to injection rate, thrombosis and thrombophlebitis.

Neurological reactions: Spasm, convulsions, aphasia, syncope, paresis, paralysis resulting from spinal cord injury and pathology associated with the syndrome of transverse myelitis, visual field losses which are usually transient but may be permanent, coma and death.

Other reactions: Headache, trembling, shaking, chills without fever, hyperthermia and lightheadedness. Temporary renal shutdown or other nephropathy.

Pediatric angiocardiography has been complicated by intramural injection with marked adverse effects on cardiac function.

During selective coronary arteriography with or without left ventriculography, patients may have clinically insignificant ECG changes. The following adverse effects have occurred in conjunction with the administration of iodinated intravascular contrast agents for this procedure: hypotension, shock, anginal pain, myocardial infarction, cardiac arrhythmias (bradycardia, ventricular tachycardia, ventricular fibrillation) and cardiac arrest. Fatalities have been reported. Complications to the procedure include dissection of coronary arteries, dislodgement of atheromatous plaques, perforation, hemorrhage and thrombosis.

Following peripheral arteriography, hemorrhage and thrombosis have occurred at the puncture site of the percutaneous injection. Brachial plexus injury has been reported following axillary artery injection.

The major causes of cerebral arteriographic adverse reactions appear to be repeated injections of the contrast material, administration of doses higher than those recommended, the presence of occlusive atherosclerotic vascular disease and the method and technique of injection. Adverse reactions are normally mild and transient. A feeling of warmth in the face and neck is frequently experienced. Infrequently, a more severe burning discomfort is observed. Transient visual hallucinations have been reported. Serious neurological reactions that have been associated with cerebral angiography and not listed under Adverse Reactions include stroke, amnesia and respiratory difficulties. Visual field defects with anopsia and reversible neurological deficit lasting from 24 hours to 48 hours have been reported. Confusion, disorientation with hallucination, and absence of vision sometimes lasting for one week have also been reported. Cardiovascular reactions that may occur with some frequency are bradycardia and either an increase or decrease in systemic blood pressure. The blood pressure change is transient and usually requires no treatment. Arthrography may induce joint pain or discomfort which is usually mild and transient but occasionally may be severe and persist for 24 to 48 hours following the procedure. Effusion requiring aspiration may occur in patients with rheumatoid arthritis. Fever and pain, cramping and tenderness of the abdomen have been reported following hysterosalpingography.

OVERDOSAGE

Overdosages may occur. The adverse effects of overdosage are life-threatening and affect mainly the pulmonary and cardiovascular systems. The symptoms may include cyanosis, bradycardia, acidosis, pulmonary hemorrhage, convulsions, coma and cardiac arrest. Treatment of an overdose is directed toward the support of all vital functions and prompt institution of symptomatic therapy.

Ioxaglate salts are dialyzable.

The intravenous LD_{50} values of HEXABRIX (in grams of iodine/kilogram body weight) were 11.2 g/kg in mice, > 8 g/kg in rats, >6.4 g/kg in rabbits and > 10.2 g/kg in dogs.

DOSAGE AND ADMINISTRATION

Details on dosage are are provided in the package insert. *CONSULT FULL PACKAGE INSERT BEFORE USE.*

Rev. Nov. 1989.

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A Randomized Pilot Trial of Brief Versus Prolonged Heparin After Successful Reperfusion in Acute Myocardial Infarction

Nathan H. Kander, MD, Kurt J. Holland, MD, Bertram Pitt, MD, and Eric J. Topol, MD

Controversy exists as to whether and how long heparin treatment is necessary after infarct vessel recanalization. To determine the role of heparin, patients with suitable angiographic features after reperfusion therapy were randomly allocated to receive a brief infusion of intravenous heparin for ≤24 hours (group 1), adjusted to a partial thromboplastin time of 2 times control or a prolonged infusion for ≥72 hours (group 2), using the same titration mechanism. Patients were excluded for complex intimal dissections, large residual filling defects, less than Thrombolysis in Myocardial Infarction grade 3 flow pattern or >50% residual stenosis. Heparin was sustained except for discontinuation 2 to 4 hours before periaccess sheath removal, or if significant bleeding (≥2 units blood transfusion) occurred. The primary endpoints were 1-week patency determined by repeat catheterization or recurrent ischemia, or both, and the incidence of bleeding complications. Fifty patients were randomized, 25 in both groups. Baseline variables were similar; 14 group 1 and 15 group 2 patients received thrombolytic treatment; 20 patients in each group had coronary angioplasty. Two documented reocclusions occurred in both groups. Significant bleeding complications occurred in 0 of 25 (0%) group 1 versus 6 of 25 (24%) group 2 patients (p <0.05). Thus, in low-risk patients after successful reperfusion, prolonged heparin therapy does not protect against rethrombosis and is associated with a significantly higher rate of bleeding complications. Therefore, prolonged heparin therapy for >24 hours does not appear to be justified in low-risk patients with successful reperfusion.

(Am J Cardiol 1990;65:139–142)

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The treatment of patients after successful reperfusion therapy in the setting of an acute myocardial infarction is unclear. In most of the major trials evaluating reperfusion therapy,[1–3] the use of intravenous heparin has been empiric because of previous anecdotal reports suggesting that the level of anticoagulation was inversely related to the frequency of recurrent ischemic events.[4,5] There have been no randomized studies analyzing whether a prolonged infusion of heparin is beneficial in maintaining infarct-related artery patency in patients after successful reperfusion therapy. As previous studies have noted that a significant risk is associated with heparin treatment in patients with underlying medical problems,[6–8] we undertook this pilot trial to determine whether the risk of heparin therapy outweighed the benefit in a group of patients felt to be at low risk of reocclusion after successful reperfusion in the setting of acute myocardial infarction.

METHODS

Patient population: From February 1987 through April 1988, 50 patients were treated with reperfusion therapy (Table I) for acute myocardial infarction and were prospectively randomized to <24 hours (group 1) or ≥72 hours (group 2) infusion of intravenous heparin. To be eligible for randomization, the patients had to have a diagnosis of acute myocardial infarction with chest pain lasting >20 minutes, unrelieved with sublingual nitroglycerin and electrocardiographic evidence of injury with ≥1 mm of ST-segment elevation in ≥2 contiguous leads. All patients required emergency cardiac catheterization and underwent reperfusion therapy.

Patients were not eligible for randomization if they had an unsatisfactory angiographic result after reperfusion therapy, which included complex dissections,[9] residual filling defects, less than Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow pattern or >50% visual estimate of residual stenosis. All patients were clinically stable at the time of periaccess sheath removal, which was ≤24 hours after acute intervention. Randomization to either a brief (<24 hours) or prolonged (≥72 hours) infusion of heparin was performed at the time of sheath removal. During this same 14-month period a total of 164 patients underwent emergency cardiac catheterization for acute myocardial infarction. The majority (69%) were excluded from the current trial either because of failure to meet prespecified angiographic criteria or clinical instability in the first 24 hours.

Catheterization procedure: Patients underwent cardiac catheterization if they met the criteria already de-

TABLE I Baseline and Treatment Characteristics

	Group 1 (n = 25)	Group 2 (n = 25)
No. male (%)	21 (84)	15 (60)
Age (yrs)	55 ± 9	54 ± 10
Infarct coronary artery		
LAD	10	10
LC	4	2
Right	11	13
Total occlusions	11	11
Thrombolytic alone	6	4
IV thrombolytics ± PTCA	14	15
Streptokinase	3	1
t-PA	6	7
t-PA and urokinase	5	7
Percent infarct vessel stenosis	30 ± 13	28 ± 12
Fibrinogen nadir (mg/dl)	170	142

There were no significant differences ($p < 0.05$) at baseline for the 2 groups.
IV = intravenous; LAD = left anterior descending; LC = left circumflex; PTCA = percutaneous transluminal coronary angioplasty; t-PA = tissue plasminogen activator.

scribed. If the patients were eligible for one of the Thrombolysis and Angioplasty in Acute Myocardial Infarction protocols, they received either tissue plasminogen activator (t-PA), urokinase or a combination of both, before emergency catheterization. Other patients received intravenous streptokinase or no thrombolytic therapy before this initial catheterization.

Using the percutaneous femoral technique, arterial and venous sheaths were inserted. At the time of obtaining vascular access, 5,000 U of intravenous heparin was administered. Initial injections of the coronary arteries were reviewed, and if an angioplasty was performed, an additional 5,000 U of heparin was administered. The patients received heparin boluses of 5,000 U hourly during the catheterization procedure.

At the conclusion of the procedure, the sheaths were secured with sutures to the access site and the patient received a heparin infusion to maintain the partial thromboplastin time at 2 times control (maximum up to 2.5 times control). The sheaths were withdrawn 24 hours after the acute catheterization. The heparin was discontinued for 2 to 4 hours before sheath removal. At this time, patients were eligible for randomization if they did not fulfill the angiographic exclusion criteria outlined previously. If the patient was randomized to a brief infusion (group 1) the heparin was not continued. Patients randomized to a prolonged infusion (group 2) were restarted receiving heparin therapy with an initial bolus of 3,000 to 5,000 U, followed by 800 to 1,200 U/hour, adjusted to maintain the partial thromboplastin time to 2 times control. Patients also received 325 mg of aspirin/day, diltiazem 30 to 60 mg 4 times/day and intravenous or oral nitrate therapy.

Patients had 12-lead electrocardiograms performed after reperfusion therapy and daily for 3 days. Creatinine kinase levels with MB isoenzyme analysis were performed every 8 hours for the first 24 hours and as clinically indicated during the hospitalization.

Endpoints evaluated during the study included chest pain felt to be ischemic in origin with documented electrocardiographic changes. Urgent recatheterization was then performed, documenting whether restenosis or reocclusion of the infarct-related artery had occurred. Reocclusion was defined as TIMI grade 0 or 1 on repeat cardiac catheterization and the percent residual stenosis was determined by caliper method. The amount and site of bleeding were also evaluated with serial hematocrits and the number of blood transfusions was recorded. A significant bleeding complication was defined as requiring ≥2 units of packed red blood cells. Patients were allowed to cross over to the other treatment group if recurrent ischemia or significant bleeding endpoints were reached.

RESULTS

Patient characteristics: The baseline clinical and angiographic characteristics of the randomized patients were similar for the 2 groups and are listed in Table I. The groups of patients randomized to a brief or prolonged infusion of heparin were comparable in age, male sex, infarct artery, type of intravenous thrombolytic agents used, number of total occlusions and percent visual estimate of residual stenosis after reperfusion therapy.

Acute reocclusions: Four patients had documented reocclusions on follow-up catheterization and were evenly divided between both groups. Three of the 4 patients had recurrent symptoms and electrocardiographic changes suggestive of ischemia before the follow-up heart catheterization, of which only 1 was successfully recanalized with angioplasty. Only 40 of the 50 patients consented to follow-up catheterization. Of the 10 patients in whom follow-up catheterization was not performed, exercise thallium scintigraphy or exercise radionuclide ventriculography was performed. There was no evidence of recurrent ischemia that would suggest restenosis in any patient.

Bleeding complications: There were no patients in group 1 who had significant bleeding (defined as the need for transfusion of ≥2 units of packed red blood cells). In group 2, 6 patients had significant bleeding, requiring discontinuation of heparin. A similar number of patients received thrombolytic agents in both groups. Of the 6 patients who had bleeding complications, 5 were women, and 5 had received thrombolytic agents before the initial catheterization. One patient received both intracoronary and intravenous streptokinase, and 1 patient received a combination of intravenous urokinase and t-PA. The other 3 had received intravenous t-PA. Sites of bleeding included the periaccess site, genitourinary (hematuria) and the gastrointestinal tract. No cases of intracerebral hemorrhages were noted.

DISCUSSION

The optimal prophylactic medical treatment after successful reperfusion therapy to maintain coronary artery patency is controversial, because in the previous trials that have used thrombolytic agents or angioplasty, or both, intravenous heparin has been continued for at least 72 hours after intervention, and usually until hospital discharge.[1–3] In the studies evaluating primary angioplasty for the treatment of acute myocardial infarc-

tion, the incidence of late reocclusion has ranged from 2 to 17%.[10–12] Treatment with intravenous thrombolysis has resulted in late reocclusions ranging from 5 to 45%.[1,13–15] Virtually all these patients have been treated aggressively with medical therapy including heparin and aspirin, and still a significant number of patients have documented reocclusion or recurrent ischemic events during the initial hospitalization.

Therefore, we have hypothesized that in those patients who have a minimal residual stenosis and who have no angiographic evidence of dissection or thrombus, there might not be additional benefit with a prolonged heparin infusion. In this group of patients, the use of heparin may be detrimental secondary to the risk of hemorrhage. We undertook this pilot trial to evaluate heparin's role in preventing reocclusion as well as the incidence of bleeding complications in patients undergoing successful reperfusion therapy.

In this randomized pilot study, the prolonged use of heparin did not appear to prevent reocclusion, as a similar proportion (8%) of patients in both groups had documented rethrombosis on follow-up catheterization. All patients had received heparin therapy for at least the initial 24 hours and the randomization was performed after this time. We attempted to eliminate patients who may have had subclinical thrombus formation at the time of the initial catheterization or who may have had recurrent ischemic events within the first 24 hours. It has been shown that with elective angioplasty and treatment with t-PA during acute myocardial infarction, recurrent ischemic events occur most frequently within the first 24 hours.[1,16] After elective angioplasty, full anticoagulation for 24 hours was found to be beneficial in patients both with and without angiographically visible thrombus present.[16] Although an angiogram may not demonstrate filling defects to be present, a residual thrombus was likely present. Therefore, in the control group, 24-hour heparin therapy was instituted. The results of our pilot study suggest that beyond this time interval, heparin does not appear to be of any added benefit in a group of patients who were at low risk of reocclusion by clinical and angiographic criteria.

A significant number of patients had bleeding complications in the group treated with prolonged heparin therapy. Greater than 20% of our patients who were treated with ≥72 hours of heparin required transfusion of ≥2 units of packed red blood cells and discontinuation of anticoagulation. Of the 6 patients with significant bleeding difficulties, 5 were women and 5 had received thrombolytic agents before the initial catheterization. All of the blood loss was confined to periaccess site bleeding or gastrointestinal or genitourinary sources. Similarly, the TIMI trial[13] reported a >15% incidence of bleeding events in both the patients treated with t-PA or streptokinase. All their patients had a pretreatment catheterization as well as subsequent prolonged intravenous heparin therapy. In the European Cooperative Study,[3] in which patients were treated with t-PA, heparin, aspirin and long-term coumadin therapy, there was a 23% incidence of significant bleeding complications in those treated without early cardiac catheterization, and a 41% incidence of bleeding in those undergoing invasive evaluation.

In our study, a similar number of patients in both groups received thrombolytic therapy. Therefore, it is of interest that only the group of patients treated with prolonged heparin therapy had significant blood loss recorded. Larger randomized studies are now being performed that will evaluate the use of prolonged heparin therapy in maintaining infarct artery patency in patients undergoing thrombolytic therapy alone. Both the Third International Study of Infarct Survival and Gruppo Italiano per lo Studio della Supravivenza Nell'Infarto Miocardioco trials are evaluating the use of high-dose subcutaneous heparin (12,500 U twice daily) in patients treated with intravenous streptokinase or t-PA and its effect on the in-hospital and long-term outcomes. If shown to be effective for reducing reinfarction, the use of subcutaneous heparin, as compared to the intravenous route, may reduce the risk of significant bleeding noted in the current and previous studies.[1,2] The recent Thrombolysis and Angioplasty in Acute Myocardial Infarction trial has demonstrated the lack of need for intravenous heparin bolus at the initiation of t-PA, and the avoidance of early heparin may also be effective in reducing hemorrhagic risk.[17]

A major limitation of our study is the number of patients. We did not attempt to detect a significant reduction in the rate of reocclusion with prolonged heparin therapy because the number of patients required to do this was beyond the scope of our study. To detect a 50% reduction in reocclusion with a 90% power, an α error of 0.05 and a β error of 0.10 would require 1,100 patients. Therefore, larger randomized control studies are needed to verify whether prolonged heparin therapy reduces the rate of reocclusion and would justify the significant bleeding risk determined in our study. The other limitations were that only 80% of our patients had a repeat coronary angiographic study at the time of hospital discharge, and we focused on a low-risk subgroup, as identified by clinical and angiographic criteria. Silent reocclusions may have occurred in the other 10 patients. Exercise tomographic thallium scintigraphy as well as exercise multigated blood pool images were performed in all these patients and no evidence of ischemia was demonstrated. This does not, however, rule out silent reocclusions with adequate collaterals. Two of these 10 patients developed recurrent symptoms of angina pectoris within 6 months, and had evidence of periinfarct ischemia on repeat thallium testing. Repeat cardiac catheterization demonstrated restenosis but not reocclusion in both these patients and repeat angioplasty was performed with resolution of the symptoms.

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The Portable Programmable Microprocessor-Driven Real-Time 12-Lead Electrocardiographic Monitor: A Preliminary Report of a New Device for the Noninvasive Detection of Successful Reperfusion or Silent Coronary Reocclusion

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Successful intravenous thrombolytic therapy early in myocardial infarction has the potential to reduce patient mortality without the additional risk and cost of aggressive invasive therapy. Noninvasive detection of successful reperfusion using resolution of chest pain, ST-segment changes assessed on static electrocardiograms, arrhythmia evolution, early isoenzyme peaking or changes in ventricular perfusion or function has been hampered by poor sensitivity or specificity, or inability to provide timely information. A newly available portable programmable microprocessor-driven real-time 12-lead electrocardiographic monitor has been introduced that may address these limitations. A continuously updated precise digital record of ST-segment activity at the bedside provides valuable information both in monitoring patients during reperfusion therapy to determine the efficacy of such treatment and in the subsequent hours to signal threatened reocclusion. This report describes the salient features of the monitor and presents 4 distinct situations in which the monitor detected timely information regarding coronary patency after reperfusion.

(Am J Cardiol 1990;65:143–148)

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Widespread use of intravenous thrombolytic agents in attempts to limit myocardial infarct size has generated interest in techniques that can determine the efficacy of such therapies.[1–6] A real-time method that could noninvasively detect successful thrombolysis and monitor patients after therapy to signal threatened reocclusion would greatly aid the clinician in deciding whether patients would benefit from additional aggressive and costly treatment.

Deviation of the ST segments on the standard 12-lead electrocardiogram has been used routinely to identify the presence of myocardial ischemia and, with less success, its anatomic location and extent. More recently, observation of the change in the magnitude of ST-segment deviation on serial electrocardiograms taken at fixed intervals during therapy has been used to determine the success or failure of thrombolysis, but with limited results.[1,6–10] This may have been due to the inability of the investigators to know the precise intervals necessary to obtain the most timely electrocardiograms for each individual patient. Further, subsequent electrocardiograms taken once daily in the cardiac care unit may not reflect the true ischemic activity of the patient.

In attempts to overcome these limitations both during the administration of the therapy and in the following hours, a real-time standard 12-lead monitor has been developed that can automatically acquire, display and store sequential electrocardiograms. This report describes the salient on-line features of the monitor, various off-line capabilities and discreet examples of its use in 4 specific clinical situations.

METHODS

Description of the electrocardiographic monitor: The EL-I (Mortara Instruments) is a portable, programmable, microprocessor-based device that can acquire, analyze and store standard 12-lead electrocardiograms at manually programmed intervals or automatically in the presence of new ST-segment changes.[11] The EL-I is an interactive monitor capable of full disclosure of either the standard 12-lead analog waveforms or a continuously updated trend of the summated ST deviation from all 12 leads over time, visible on a liquid crystal display when activated with a button push. All data from the EL-I can be downloaded to a standard

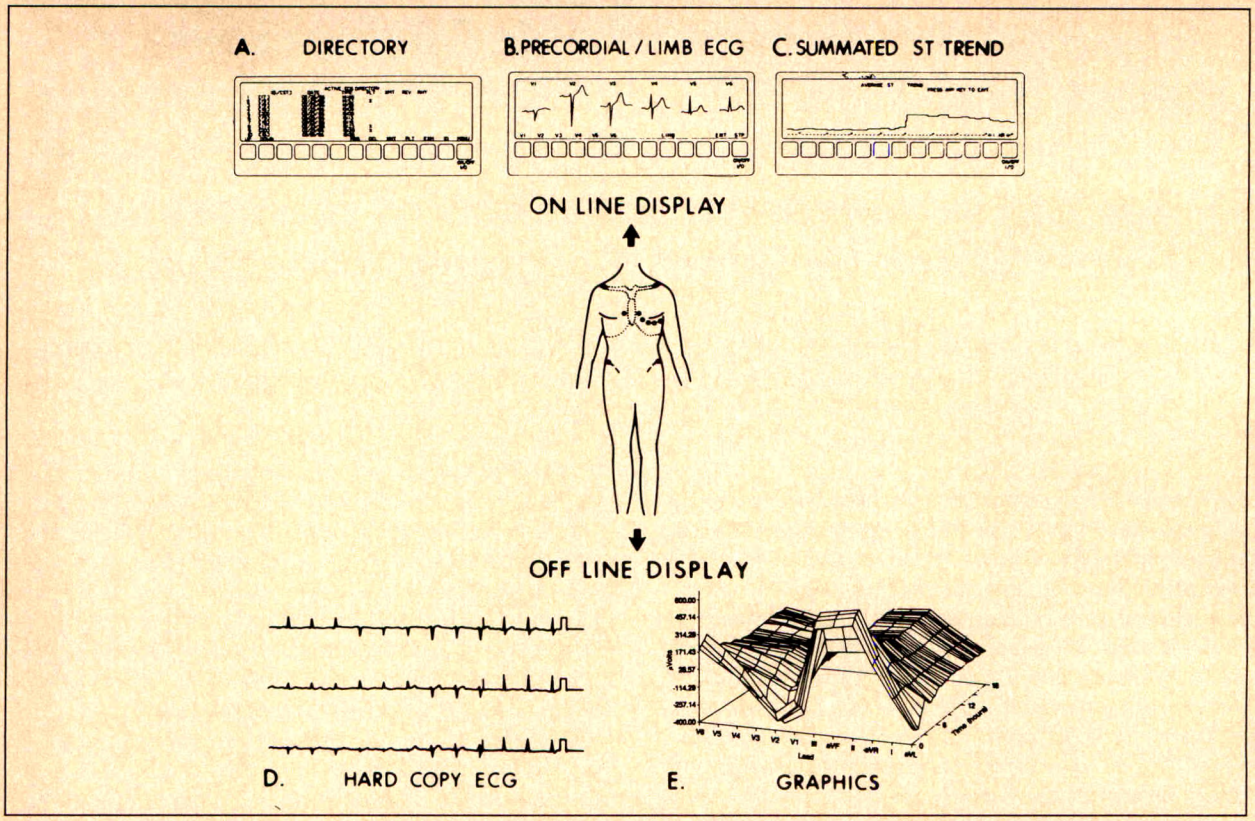


FIGURE 1. Salient features of the EL-I monitor. The limb leads (*closed circles*) are positioned on the torso for optimal noise reduction; the precordial leads are in the standard positions. The on-line features include a directory (*A*) of the patient's electrocardiographic frequency including date and time. From this directory, any electrocardiogram can be selected and displayed on the monitor screen (*B*). The limb leads (I, II, III, aVR, aVL and aVF) and the precordial leads (V_1 to V_6) are viewed on separate screens. The summated ST-segment trend (*C*) can be viewed at any time. The off-line features include hard copies of electrocardiograms (*D*) selected from the directory, which are obtained by downloading stored data to a Hewlett Packard Plotter. Retrospective analysis of the ST-segment trend can be displayed 3-dimensionally (*E*) from existing personal computer-based software analysis of data downloaded from the EL-I.

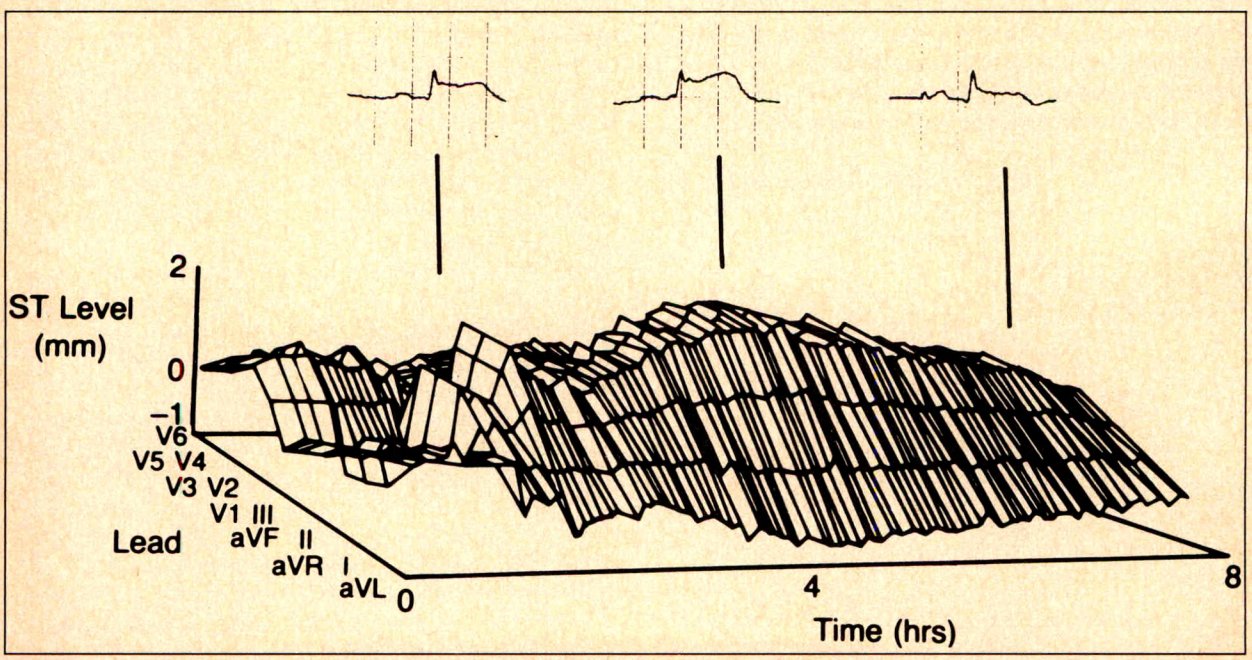


FIGURE 2. Asymptomatic occlusion after elective angioplasty. Three-dimensional graphic output from personal computer-based software analysis of the EL-I electrocardiograph showing ST level (*Y axis*) in all 12 standard leads (*Z axis*) over time (*X axis*). Rotation favors appreciation of multilead ST-segment "fingerprint," which is identical during angioplasty and in the subsequent spontaneous right coronary artery occlusion. Analog beats from lead aVF are from the continuous electrocardiographic record. The patient reached a steady state approximately 6 hours after angioplasty.

personal computer for further analysis or archival storage.

The electrocardiograph is 2 inches × 6 inches × 12 inches in size and weighs 2.9 pounds. Use of digital sampling and filtering techniques similar to those on many standard electrocardiographic carts allows a flat frequency response of 0 to 100 Hz with no phase shift distortion. Electrocardiograms are recorded by sampling electrical potentials simultaneously at 4-ms intervals from all 12 leads over a 10-second period at a resolution of 2.5 mV.

Whereas most electrocardiographic monitors discriminate wave boundaries and beat types from only single- or dual-lead input, the EL-I uses digital, simultaneous 12-lead technology to determine the dominant cycle configuration and form a representative QRS complex. These noise-reduced complexes help to distinguish QRS onset and offset as the earliest and the latest deflections in any one of the simultaneously recorded leads,[12] thus facilitating precise quantitation of the waveforms. Using these reference points, the ST segments are measured at the J point + 60 ms. For optimal noise reduction, the limb leads are positioned on the torso; the precordial leads are in the standard positions (Figure 1).

The device may be operated in either of 2 ST-segment modes: "monitoring" or "surveillance." In monitoring mode, the device acquires and stores electrocardiograms at programmable intervals from every 20 seconds to every hour. In surveillance mode, the operator preprograms a threshold that defines the magnitude of ST-segment change considered to be abnormal, such as a 2-mm change in a single lead or a 1-mm change in 2 leads. The device acquires and stores a baseline electrocardiogram. A subsequent electrocardiogram is taken 30 seconds later and compared to the baseline. If it is within the preset threshold, the process continues. If 2 consecutive electrocardiograms show ST-segment abnormality, however, the device stores those 2 records and all subsequent electrocardiograms at 30-second intervals over the next 3 minutes, documenting the event at "high resolution." The last electrocardiogram of this series is used as the new baseline for subsequent surveillance mode comparisons. An alarm option may be selected that sounds at the bedside when such persistent ST abnormalities are detected.

During normal operation of the monitor, a directory of the patient's electrocardiographic frequency, including date and time, can be visualized with a button push (Figure 1A). From this directory any electrocardiogram may be selected and displayed on the monitor screen (Figure 1B). The limb leads (I, II, III, aVR, aVL and aVF) and the precordial leads (V_1 to V_6) are viewed on separate screens. At any time, a trend of the average ST

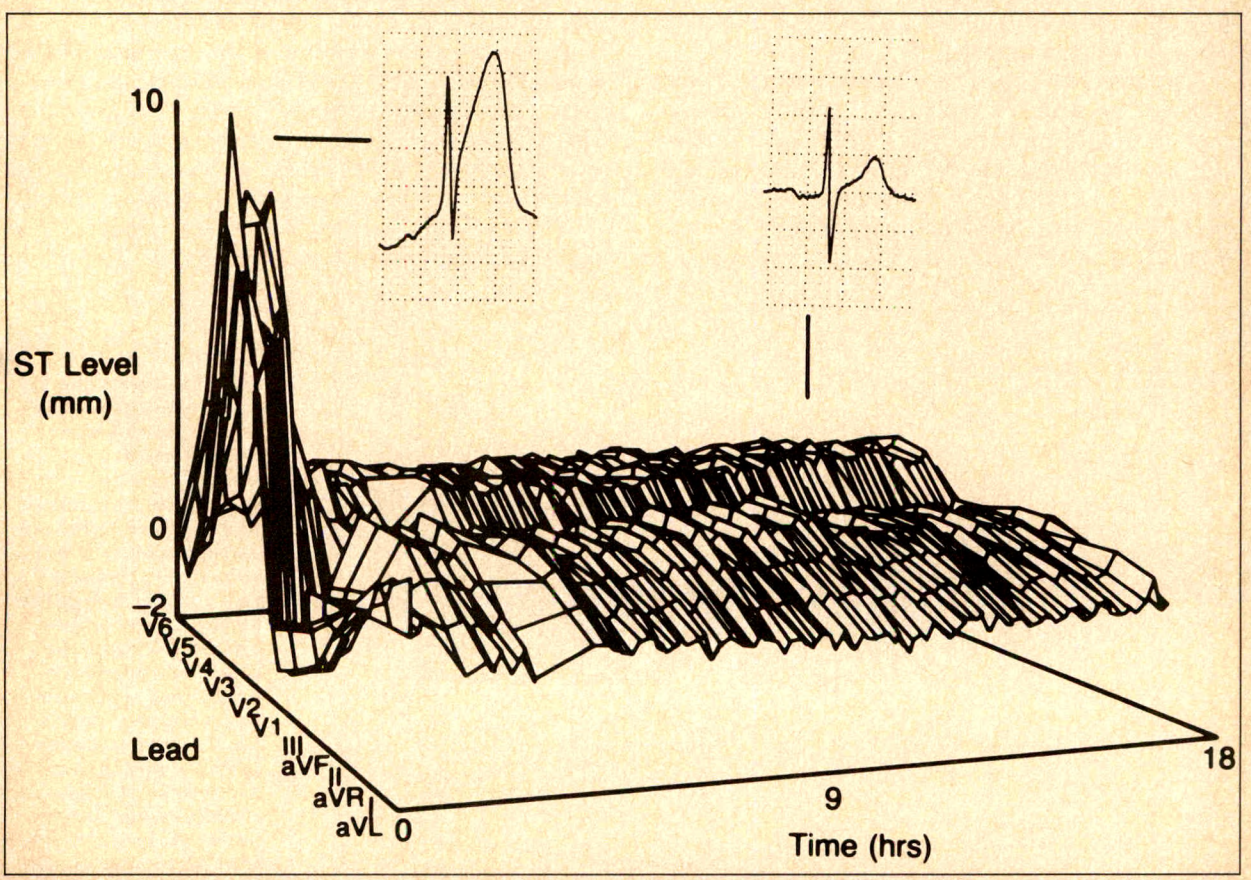


FIGURE 3. Persistently successful reperfusion of an acute infarct. Graphic format as in Figure 2. ST-segment "fingerprint" of left anterior descending occlusion shows anterolateral ST elevation with reciprocal inferior ST depression. Analog beats from lead V_2 from the continuous electrocardiographic recording taken during the angioplasty are shown. The patient reached a steady state approximately 20 minutes after the angioplasty.

magnitude can be viewed at the bedside. The average ST magnitude is the normalized sum of the absolute ST levels from each of the 12 leads (summated ST trend). The horizontal, or time, axis of the ST trend on the monitor screen is segmented into 1-hour divisions (8 hours total) with the time increasing from left to right. The vertical axis ranges from 0 to 500 mV (Figure 1C).

The EL-I monitor also has clinically valuable off-line capabilities. A "hard copy" standard 12-lead electrocardiogram selected from the patient directory (Figure 1D) can be obtained by downloading the stored data to a Hewlett Packard Plotter. Further, retrospective analysis of the ST-segment trend can be displayed 3-dimensionally for each of the 12 leads (inverse aVR) over time (Figure 1E). These graphics are easily generated from existing personal computer-based software analysis of data downloaded from the EL-I (Interventional Cardiology Associates).

Clinical applications of the monitor: The features of the EL-I electrocardiograph have made it especially suited for monitoring the ischemic activity in patients during reperfusion therapy and in the following hours in the cardiac care unit. This report focuses on 4 distinct situations in which the EL-I monitor detected valuable clinical information regarding coronary patency after thrombolysis: asymptomatic occlusion after elective angioplasty, persistently successful reperfusion of an acute infarct, symptomatic reocclusion after reperfusion of an acute infarct and asymptomatic reocclusion after reperfusion of an acute infarct.

Asymptomatic occlusion after elective angioplasty: A 57-year-old man underwent successful elective angioplasty of a right coronary artery 5 days after receiving intravenous streptokinase. The EL-I monitor during the procedure revealed inferior ST-segment changes (Figure 2). Though he remained asymptomatic, retrospective analysis of the EL-I data showed ST elevation in leads II, III and aVF identical to the pattern seen during angioplasty. Repeat angiography showed a completely occluded right coronary artery.

Persistently successful reperfusion of an acute infarct: A 52-year-old man presented after 1 hour of chest pain onset, with ST-segment elevation in leads I, aVL and V_1 to V_6. The patient was taken immediately to the cardiac catheterization laboratory where an occluded left anterior descending artery was demonstrated and successfully treated with angioplasty. The EL-I showed that the ST-segment activity reached a steady state within 20 minutes after reperfusion, with no further activity during monitoring (Figure 3).

Symptomatic reocclusion after reperfusion of an acute infarct: A 60-year-old man presented with 2.5 hours of chest pain and ST elevation in leads II, III and aVF. He was given intravenous streptokinase and taken immediately to the cardiac catheterization laboratory. Emergent angioplasty of a completely occluded right coronary artery was successful. Six hours later the EL-I alarm triggered, and chest pain woke the patient. Immediate viewing of the EL-I screen showed ST-segment changes in the leads identical to those that had shown activity during angioplasty (Figure 4). With medication, the patient's angina subsided and the ST-segment changes resolved. Fourteen hours after angioplasty, the EL-I was triggered again by recurrent ST elevation. Follow-up catheterization performed 10 days later showed an occluded right coronary artery.

Asymptomatic reocclusion after reperfusion of an acute infarct: A 63-year-old man received intravenous streptokinase in a community hospital 1.5 hours after onset of chest pain. The patient stabilized over the next several hours. The following day he had recurrent chest pain associated with transient ST elevation in leads II, III and aVF. He was transferred for elective angioplasty. The night before the procedure, the EL-I alarm

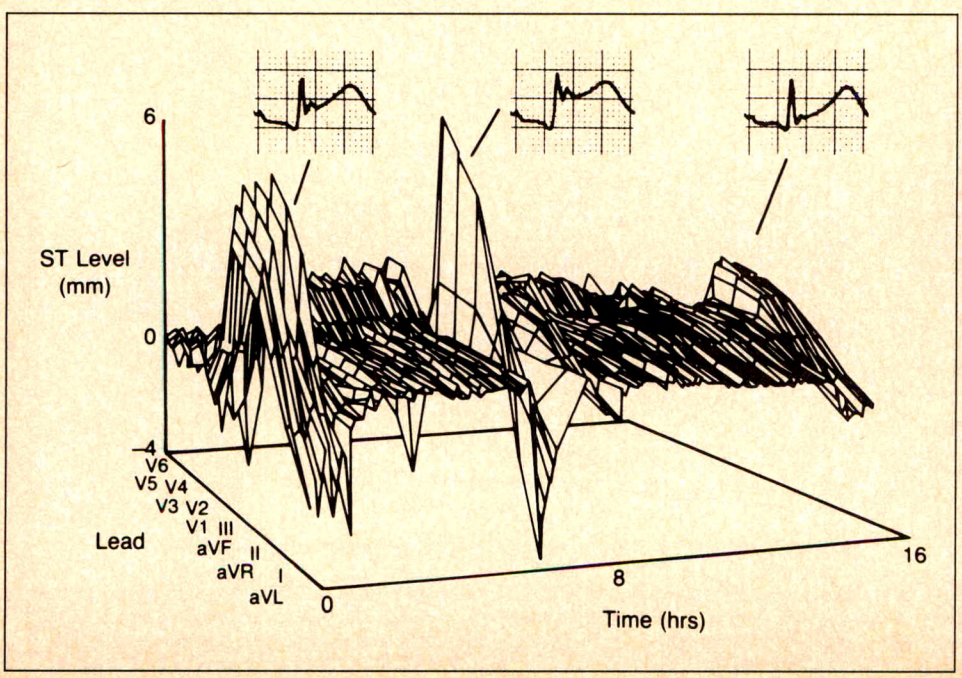


FIGURE 4. Symptomatic reocclusion after reperfusion of an acute infarct. Graphic format as in Figure 2. ST-segment "fingerprint" of right coronary artery occlusion seen during angioplasty recurs twice during coronary care unit monitoring. The second coronary care unit episode (14 hours) shows minimal ST-segment recovery, suggesting persistent reocclusion despite the absence of symptoms in the sedated patient, later confirmed at follow-up catheterization. Analog beats from lead aVF are from the continuous electrocardiographic record.

triggered during several episodes of transient ST elevation (Figure 5). The patient was awakened and reported only nausea. Urgent catheterization showed a proximal occlusion of the right coronary artery and angioplasty was performed.

DISCUSSION

Intravenous thrombolytic therapy is desirable for the limitation of infarct size because it can be given early and requires no specialized equipment. In the best of circumstances, however, 19 to 69% of patients will not reperfuse with this therapy alone, depending on the agent, the timing and the dosage.[13–16] Of the patients who do reperfuse, 14 to 50% will develop ischemia or suddenly reocclude the infarct vessel, often in the absence of symptoms, while in the cardiac care unit.[15,17–19] Such patients would require further aggressive treatment, because failed thrombolysis or reocclusion after successful thrombolysis is associated with greater impairment of left ventricular function and increased early and late mortality.[13,14,18,20,21] Use of a device, such as the EL-I monitor, could provide timely identification of these patients, thus accelerating the administration of additional therapy. The EL-I could also spare those patients with successful reperfusion the risk and cost of further unnecessary treatment.

The use of ST-segment changes as noninvasive markers of reperfusion has had mixed results, due in part to the limitations inherent in obtaining static electrocardiograms at fixed and infrequent intervals. In the Thrombolysis In Myocardial Infarction experience, electrocardiograms taken 6 hours apart were unable to distinguish between patients with successful versus unsuccessful reperfusion.[6] Comparing admission ST levels with those at 90 minutes after thrombolytic therapy, Califf et al[1] found ST recovery to be a highly specific but very insensitive marker of angiographically confirmed reperfusion, similar to the findings of Kircher et al.[2]

Evaluation of the ST-segment changes on continuous, rather than static, electrocardiographic recordings has increased sensitivity and specificity for the detection of coronary patency.[7,22–24] The continuous format can reflect even transient ST changes by using each patient as his own baseline. As previously reported,[25] and as evidenced by several of the patients detailed in this report, dramatic ST-segment alterations that reflect either coronary occlusion or reperfusion can occur within seconds. Hence, it is likely that static electrocardiographic sampling over fixed intervals may miss the peak ST activity and incompletely assess the ongoing rate of ST change, both of which are valuable clinical markers. Further, because the isoelectric ST level is not achieved immediately even with successful reperfusion,[22] determination of an individual patient's steady ST-segment state requires a patient-specific reference point. Whereas static electrocardiograms are able to reveal whether there is relative ST-segment improvement, it is important for the clinician to be able to judge whether such improvement has stabilized or is still improving to optimally determine the patient's response to the therapy.

It has been shown previously that 3-lead Holter monitor acquisitions during both elective angioplasty and infarction provide a template or "ST-segment fingerprint" that is both coronary and patient specific.[26] Such "fingerprint" patterns have been valuable for detection of high-risk patients, even in the complete absence of symptoms. The 12-lead format of the EL-I would augment this information. Combined with its real-time capability, the EL-I may contribute unparalleled noninvasive information about the efficacy of emergent thrombolytic therapy at the bedside. Thus, rather than using an arbitrary limit of ST deviation to detect abnormality in a limited number of leads, the EL-I could be programmed to detect abnormality using all 12 leads based on a match to the known ST fingerprint of the individual patient. In the event of a strong correlation with the infarction pattern, the device could

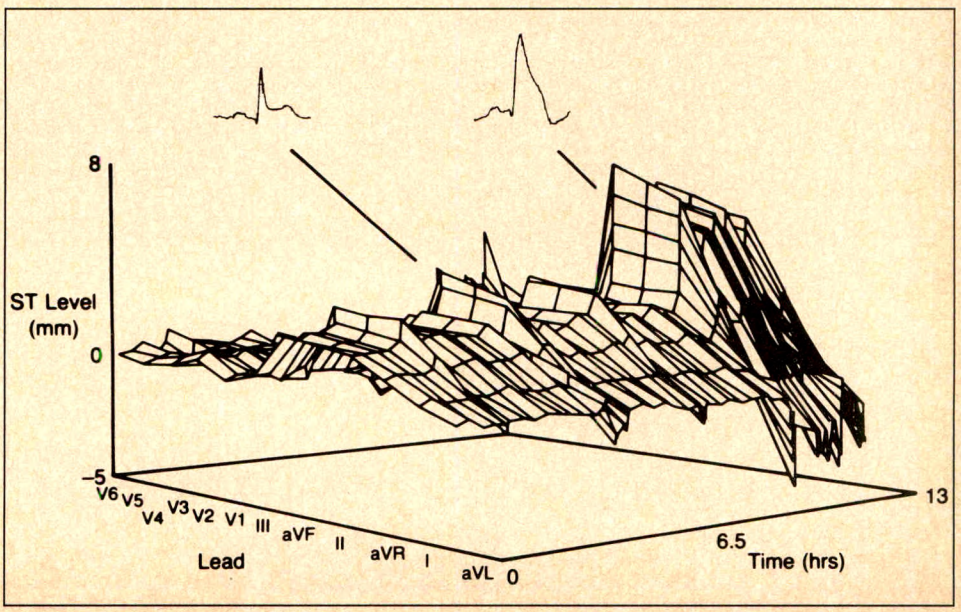


FIGURE 5. Asymptomatic reocclusion after reperfusion of an acute infarct. Graphic output as in Figure 2. ST-segment "fingerprint" from all ischemic episodes shows the inferior injury pattern of right coronary occlusion. The persistent ST elevation at 6 hours led to urgent catheterization, confirming closure of the previously reperfused right coronary artery. All ischemic episodes and the coronary occlusion occurred in the absence of symptoms. Analog beats from lead aVF are from the continuous electrocardiographic record.

potentially detect abnormality and alarm as low as 0.2 mm of change.

Continuous electrocardiographic monitoring has often been limited to devices that may have poor electronic fidelity, a limited number of leads and delayed analysis. This report describes a newly available monitor that affords real-time capability with simultaneous 12-lead acquisition using microprocessor-driven electronics whose full value in clinical applications is only beginning to be tested. Its usefulness appears to be in the setting of reperfusion therapies, both as a marker of successful reestablishment of coronary flow and as a coronary care unit monitor for enhanced detection of recurrent ischemia due to sudden reocclusion of the infarct-related vessel.

Acknowledgment: We would like to acknowledge the unending support of the staff in the Cardiac Catheterization Laboratory and the Coronary Care Unit at Georgetown University Hospital, as well as the extensive technical assistance of Joseph DeMichele and Harry Newman, graphic artist. We also extend special appreciation to Sylvester Cherry for preparing the manuscript.

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Predischarge Maximal Exercise Test Identifies Risk for Cardiac Death in Patients with Acute Myocardial Infarction

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A maximal exercise test was performed in 54 patients with acute myocardial infarction (AMI) before discharge and in 49 age-matched control subjects. The long-term prognosis was assessed after an average follow-up of 7.6 years in AMI patients and 5.8 years in control subjects. The maximal work capacity and systolic blood pressure increase in AMI patients was 59% that of control subjects ($p < 0.001$). Seventeen AMI patients had significant ST-segment shifts, 13 with ST depression and 4 with ST elevation. In AMI patients experiencing a cardiac death during follow-up the maximal work capacity and systolic blood pressure increase were significantly lower than in survivors and those who died from noncardiac reasons ($p < 0.01$; $p < 0.05$), with no difference between these groups in the number of patients with ST-segment shifts. The average maximal work capacity of control subjects was 143 watts. A maximal work capacity half this (≤72 watts) predicted long-term mortality in AMI patients ($p < 0.001$). In addition a low increase in systolic blood pressure (<30 mm Hg) also predicted long-term mortality ($p < 0.005$), whereas ST shifts were of no significant value. In this study maximal work capacity turned out to be the best single exercise variable for identifying groups of AMI patients with very low and relative high risk of cardiac death. When all 3 exercise variables were combined, the predischarge maximal exercise test was of great value in identifying AMI patients at low risk for cardiac death (predictive value of a negative test: 95%).

(Am J Cardiol 1990;65:149–153)

Risk stratification of survivors of myocardial infarction offers 2 major benefits. High-risk patients can be identified for closer medical follow-up and further diagnostic and therapeutic procedures can be instituted to alter their poor prognosis. Patients at low risk may be spared needless invasive studies and unwarranted physical restrictions.

The prognostic value of early exercise testing after acute myocardial infarction (AMI) has not been adequately established. Only few investigators have shown a positive correlation between the development of significant ST-segment depression and 1-year[1] as well as long-term mortality.[2] Several investigators have demonstrated that ST-segment depression is significantly prognostic for subsequent cardiac events.[3–10] However, other investigators have not been able to find this relation.[11–15] Davidson and DeBusk[7] found a maximal workload <4 METs predictive of subsequent cardiac events in patients without significant ST depression or angina pectoris during exercise testing after AMI. Other investigators have noted that patients with a low maximal workload have an increased risk of subsequent cardiac events[15] or long-term mortality.[16] However, Fioretti et al[14] found no difference in work capacity between survivors and nonsurvivors of AMI. Finally, a low increase or decrease in systolic blood pressure during exercise testing early after AMI has been predictive of future cardiac events[6,10] or mortality.[3,14,17] Again, these results have been contradicted by others.[2,9]

This study aims to clarify the following questions about a maximal exercise test performed before discharge by patients with AMI: By how much do decreases in maximal work capacity in AMI patients differ from an age-matched randomly selected control group? What is the long-term prognostic value of maximal work capacity, systolic blood pressure increase and ST-segment shifts?

METHODS

Patients: During a 15-month period ending in 1978, 61 consecutive patients <67 years of age experienced AMI. Seven were excluded (3 did not want to participate, 1 was referred to another hospital and 3 were unable to exercise due to orthopedic problems). Only 3 of the remaining 54 patients were women.

Control subjects: The control subjects were age-matched men randomly selected from the municipal register. Of the 61 contacted by letter and telephone, 49 were included and performed the exercise test during the months of January and March 1980. Twelve were

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excluded (6 did not want to participate, contact was not established with 3 and 3 were excluded for noncardiac reasons).

Study procedure: AMI patients and control subjects performed a maximal exercise test on a bicycle ergometer (Siemens-Elema), beginning with 50 watts (3.3 METs) for 6 minutes, and with increments of 50 watts every 6 minutes until exhaustion or other reasons for stopping the test.[18] In women the workload given was half that of men. Cuff systolic blood pressure was obtained before exercise, in the last minute of each exercise stage, at maximal exercise and at 1, 2 and 10 minutes in the recovery phase. An electrocardiogram (V_1, V_5, V_6) was recorded simultaneously with the blood pressure measurements. The exercise tests were carried out when the patients were ready for discharge. All prescribed medications were maintained during the exercise tests. Maximal work capacity was expressed as maximal watts calculated as previously described.[19] Low work capacity of AMI patients was defined as up to half the mean value of control subjects. Cardiovascular response was expressed as an increase in systolic blood pressure. An increase in systolic blood pressure of <30 mm Hg was defined as a low blood pressure response. An ischemic response was defined as ST-segment shifts of ≥1 mm. The predictive value of a positive and a negative test was evaluated for each variable, and for the combined variables.

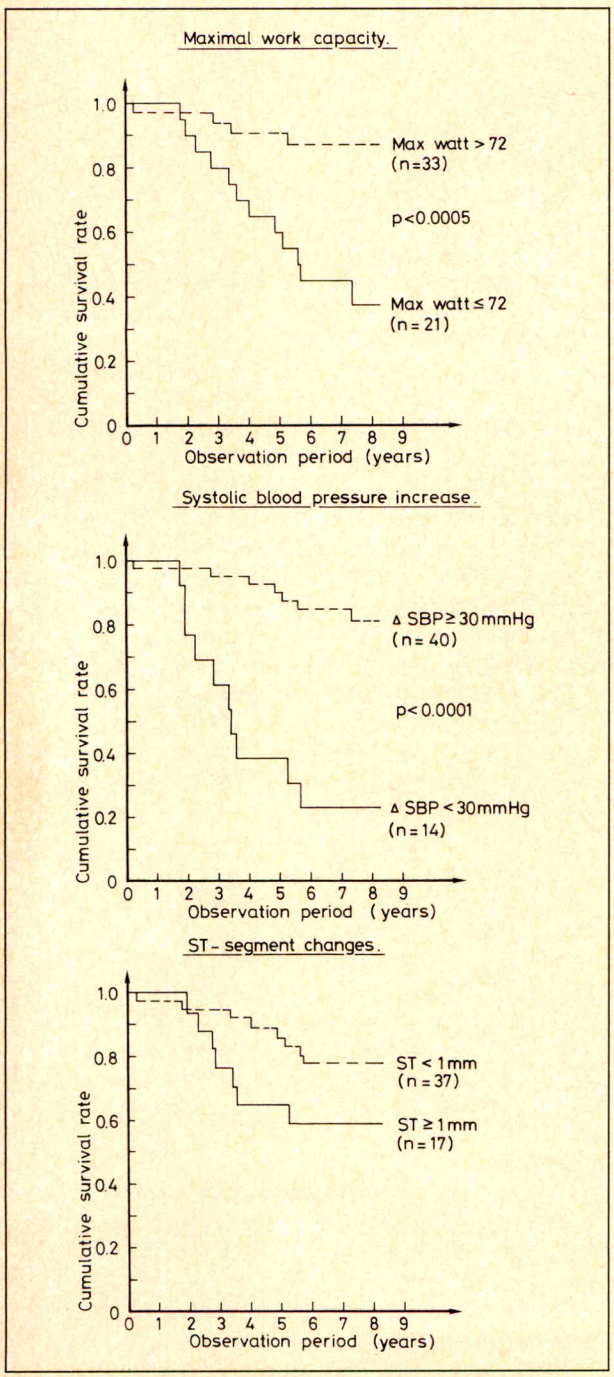


FIGURE 1. Kaplan-Meier analysis demonstrates that low maximal work capacity (Max watt) and low systolic blood pressure increase (Δ SBP) at maximal exercise test predischarge are related to significant cumulative probability of cardiac death. This was not the case for ST-segment shifts.

Data handling and statistical procedures: Data were collected on precoded forms and entered into a computer file. The Student *t* test was used to compare mean values and a chi-square test was used to compare incidences of discrete variables between groups. Kaplan-Meier analyses were used to demonstrate if exercise variables were correlated with a significant cumulative probability of cardiac death. A p value <0.05 was deemed significant.

RESULTS

Acute myocardial infarction: PREDISCHARGE: The mean age of the patients was 55 ± 8 years. Thirteen patients (24%) had had a previous myocardial infarction. The mean duration of hospitalization was 20 ± 6 days, with a maximal lactic dehydrogenase (LDH) of 1,441 ± 981 U/liter. The AMI was complicated by ventricular fibrillation in 13%, heart failure in 9%, angina pectoris in 6%, atrioventricular block in 4% and supraventricular tachycardia in 6%. No significant differences between the AMI subgroups were found in incidence of previous infarction, duration of hospitalization, maximal LDH and complications. Twenty-one patients were treated with cardioactive drugs: digoxin (13 patients), β-blocking agents (8 patients) and calcium antagonists (3 patients). Twenty-nine percent of survivors had been treated with at least 1 of these agents; in those with the endpoints of cardiac and noncardiac death 69 and 14%, respectively, were treated with at least 1 of these agents. This difference was not significant (p <0.08).

Follow-up: Sixty-six cardiac events occurred in 33 of the AMI patients during 7.6 ± 4 years of follow-up. Thus, a cardiac death occurred in 16, noncardiac death in 7, 16 episodes of reinfarction in 14, 20 episodes of unstable angina pectoris in 15 and 7 episodes of cardiac failure in 5 patients.

Exercise test: The exercise variables for the control subjects and for the AMI subgroups specified for survivors and those who died from cardiac or noncardiac

TABLE I Exercise Variables from AMI Patients, AMI Subgroups and Control Subjects

	AMI Subgroups				
	Total	Cardiac Death	Noncardiac Death	Survivors	Control Subjects
No. of subjects	54	16	7‡	31§	49
Maximal work capacity (watts)	84 ± 32*	62 ± 27†	90 ± 34	94 ± 29	143 ± 42
Systolic blood pressure increase (mm Hg)	45 ± 20*	30 ± 15	50 ± 30	50 ± 20	75 ± 25
No. of subjects with ST-segment shifts (%)	17 (31)	8 (50)	1 (14)	8 (26)	3 (6)

* p <0.01 patients vs control subjects; † patients with cardiac death in the follow-up period vs survivors; ‡ 6 men and 1 woman; § 29 men and 2 women.
AMI = acute myocardial infarction.

deaths during follow-up are listed in Table I. The AMI patients had a maximal work capacity 59% that of the control subjects, and a systolic blood pressure increase 59% of the control subjects. Thirty-one percent of the AMI patients had significant ST-segment shifts compared to 6% of the control subjects. Those who died from cardiac reasons at follow-up had a maximal work capacity 43% of the control subjects, and a systolic blood pressure increase 38% of the control subjects. Fifty percent of the patients had significant ST-segment shifts. The exercise variables were almost equal between AMI survivors and those who died from noncardiac reasons (Table I). Reasons for stopping the exercise test for AMI patients and control subjects are listed in Table II. Serious complications such as VT, VF and death were not observed. Ninety-six percent of the control subjects had a maximal work capacity >100 watts. No significant correlation was found between maximal work capacity and maximum LDH (r = 0.01, difference not significant, n = 49).

TABLE II Reasons for Stopping the Exercise Test in AMI Patients and Control Subjects

	AMI (%)	Control Subjects (%)
Fatigue	54	67
Dyspnea	24	29
Angina pectoris	9	2
Arrhythmias	5	0
Electrocardiographic changes	4	0
Other	4	2

Prediction of long-term mortality: In patients with a maximal work capacity ≤72 watts, cardiac deaths occurred in 60%, and in patients with maximal work capacity >72 watts cardiac deaths occurred only in 11% (Table III). In patients with a systolic blood pressure increase <30 mm Hg cardiac deaths occurred in 64% and in patients with a blood pressure increase ≥30 mm Hg cardiac deaths occurred only in 18%. In patients with significant ST-segment shifts cardiac deaths occurred in 47%, compared to 23% in those with no significant ST changes. Kaplan-Meier analysis demonstrated that low maximal work capacity and low systolic blood pressure response were correlated with significant cumulative probability of cardiac death (Figure 1). This was not the case for ST-segment shifts (Figure 1). Fig-

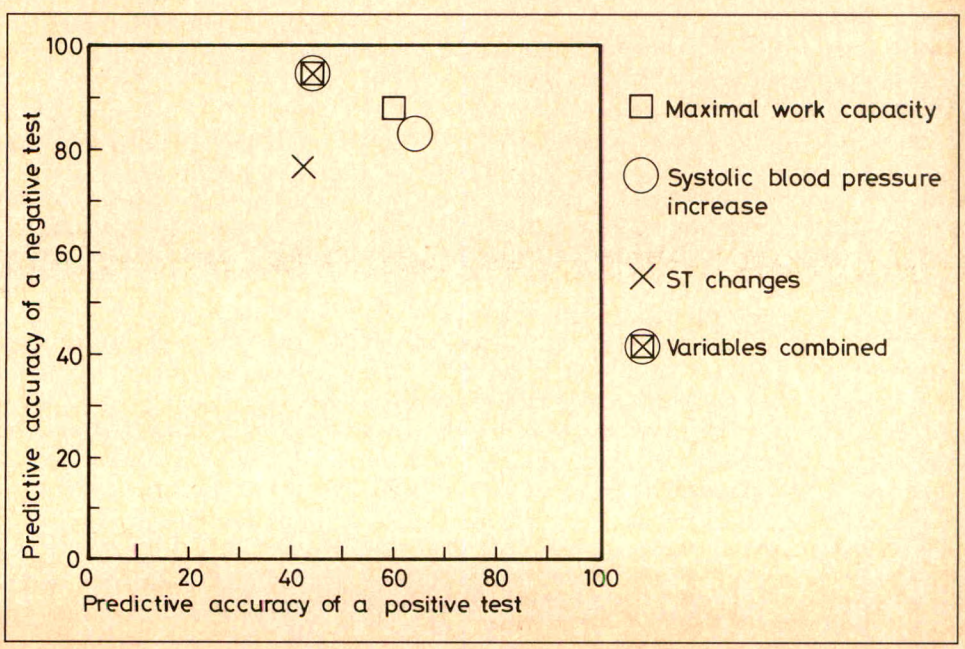


FIGURE 2. The accuracy of a positive and negative predischarge exercise test for predicting long-term cardiac mortality in acute myocardial infarction (AMI) patients.

TABLE III Predischarge Exercise Variables Predict Long-Term Mortality*

	Cardiac Death	Noncardiac Death	Survivors	p Value
Maximal watts				
≤72	12	2	6	<0.001
>72	4	5	25	<0.001
Systolic blood pressure increase (mm Hg)				
<30	9	2	3	<0.005
≥30	7	5	28	
ST-segment changes (mm)				
≥1	8	1	8	NS
<1	8	5	22	
Combined variables				
Positive test	15	4	15	<0.001
Negative test	1	3	16	

* A negative test occurred when none of the following variables were present: maximal watts ≤72 watts; systolic blood pressure increase <30 mm Hg; and significant ST-segment shifts.
NS = not significant.

ure 2 shows the predictive accuracy of a positive and negative test when maximal work capacity, systolic blood pressure increase and ST-segment shifts were evaluated separately or in combination. The predictive accuracy of a negative test for the exercise variables is fairly high (77 to 88%), especially for the combined exercise variables (95%). Such a low risk was found in 37% of AMI patients in this study (Table III).

Control subjects: INITIAL: The mean age of the control subjects was 55.8 years. Previous AMI was reported in 2, angina pectoris in 3, hypertension in 5 and chronic pulmonary disease in 5 of them. Three were treated with digoxin and 3 with β-blocking agents. Six subsequent cardiac events occurred in 5. Two subjects had a nonfatal AMI, 1 was hospitalized due to angina pectoris and cardiac failure and 2 died from noncardiac reasons.

DISCUSSION

Although maximal exercise testing has rarely been used before hospital discharge, this type of exercise test has been shown to be safe in this and other studies.[20,21] In some studies patients who could not exercise for the expected duration of their protocol had an increased mortality risk over the next year.[15,22,23] If, however, they could go the full duration of a submaximal workload, the risk was very low. Although these studies seem able to define low- and high-risk groups, no information is given concerning the maximal work capacity of the AMI patients, and their work capacity is not compared to the normal population. Knowledge of these data may have important psychological benefits for patients and help cardiologists in the development of postdischarge guidelines for exercise prescription. Finally, maximal work capacity might elicit further prognostic information.

In other studies of normal populations that were age-matched to AMI patients, a maximal work capacity >100 watts was found in 92%[24] and 95%.[25] This is in accordance with the findings of 96% in our control group. Our study showed that AMI patients had a maximal work capacity of 59% that of the control subjects. However, patients with endpoints of cardiac death had a maximal work capacity of 43% of control subjects. In survivors and those with an endpoint of noncardiac death, maximal work capacity was 66 and 63%, respectively. These results imply that a low maximal work capacity before discharge may be of prognostic value. When a low maximal work capacity was defined as ≤50% that of control subjects a Kaplan-Meier analysis showed that low maximal work capacity actually was correlated with a significant cumulative probability of cardiac death. Thus, a predischarge maximal work capacity may be of great clinical value in identifying patients with low and high risk of future cardiac death. A low maximal work capacity may be the result of a decreased left ventricular function. This is in accordance with several other studies showing that a low left ventricular ejection fraction after AMI is correlated with future coronary events[26,27] and mortality as sole endpoint.[13,14,17]

Myocardial function can also be judged by exercise-induced blood pressure response. In accordance with Fioretti et al,[14] our results suggest that inability to increase systolic blood pressure by at least 30 mm Hg expresses poor myocardial function, and significantly predicts long-term mortality (Figure 1). In several other studies the lack of adequate blood pressure response early after AMI was associated with an increased 1-year mortality[13,15,17] and an increase in coronary events.[6,10]

The bad prognosis associated with exercise parameters indicating a poor left ventricular function may be caused by large infarcts or may be due to myocardial ischemia caused by multivessel disease.[28]

In our study 6% of control subjects and 26% of survivors had significant ST-segment shifts and a low risk of cardiac death. The ST-segment changes in this group

may therefore be caused by myocardial ischemia due to minor coronary stenoses or good collateralization. Although when compared to survivors maximal work capacity and systolic blood pressure response were significantly decreased in patients with the endpoint of cardiac death, significant ST-segment shifts were not. However, 50% of these patients had significant ST-segment shifts. This indicates that at least some of the patients with bad left ventricular function variables during exercise may have a bad prognosis not due only to larger infarctions, but also due to multivessel disease. In accordance with this thesis no significant correlation was found between maximal LDH and maximal work capacity.

However, some of the patients with ST-segment changes had increased ST elevations. These changes may be proportional to the size of the infarction,[29,30] and ST elevation appears to be a bad prognostic marker,[29,30] even though this conclusion has been anticipated by others.[9,10]

This study has shown that in consecutive survivors of AMI a predischarge maximal exercise test is a safe and effective diagnostic procedure for identifying patients with low and high risk of cardiac death. When the exercise variables are combined, the predischarge maximal exercise test seems to be of great clinical value, especially in identifying AMI patients at low risk, the predictive accuracy of a negative test being 95%. Such a low risk was found in 37% of AMI patients in this study. These patients may not require either coronary angiography or β-blocking agents. Furthermore, the predischarge exercise test can be used to guide cardiac rehabilitation and bring to the patient important psychological benefits, decrease the period of convalescence and improve the return-to-work rate. The AMI patients at high risk should be followed in outpatient clinics and may require various types of medical treatment such as β blockers and even coronary angiography with a view of revascularization procedures.

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Clinical and Prognostic Significance of Lung Thallium Uptake on Rest Imaging in Acute Myocardial Infarction

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Exercise-induced pulmonary uptake of thallium-201 in patients with ischemic heart disease is probably due to transient pulmonary edema and left ventricular failure induced by exercise. The significance of increased lung uptake of thallium-201 at rest after acute myocardial infarction (AMI) has not been described. Ninety-six patients admitted with chest pain for suspected AMI or unstable angina underwent thallium-201 imaging at rest. Using conventional diagnostic criteria, 62 had AMI, 12 had unstable angina and 22 had neither. Increased lung uptake of thallium-201 was present in 24 of the total 96 (25%) patients, 20 of the 62 (32%) patients with AMI and 4 of 34 (13%) patients with no evidence of infarction. In the AMI group, those with increased lung thallium-201 uptake had a higher mean ± standard deviation segmental thallium-201 defect score (22 ± 7 vs 12 ± 8, p <0.0001), lower ejection fraction (35 ± 14 vs 49 ± 14%, p <0.002), higher peak creatine kinase levels (2,410 ± 1,247 vs 1,496 ± 1,228 IU/liter, p <0.01), higher wall motion abnormality score (25 ± 13 vs 13 ± 12, p <0.0001), increased incidence of clinical in-hospital heart failure (15 of 20 vs 7 of 42, p <0.0001) and higher short-term mortality (4 of 20 vs 1 of 42, p <0.02) compared to those without increased lung thallium-201 uptake. On stepwise discriminant function analysis, congestive heart failure emerged to be the most important determinant (F = 33.3) and thallium-201 defect score to be the most important correlate (F = 20.07) of abnormal lung thallium-201 uptake. The finding of increased lung thallium-201 uptake may complement the clinical information derived from rest thallium-201 imaging during AMI and may be used for the assessment of acute infarction-limiting interventions.

(Am J Cardiol 1990;65:154–159)

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Increased lung uptake of thallium-201 during exercise testing has been observed in patients with coronary artery disease.[1–4] This finding correlates with the severity of underlying coronary artery disease and the degree of impairment of left ventricular function.[2–5] Recent studies have shown that exercise-induced lung thallium-201 uptake has significant prognostic implications in patients with coronary artery disease.[6,7] Patients with abnormal lung thallium-201 uptake during exercise show a higher mortality and adverse cardiac events during follow-up compared to those without this finding.[6,7] Previous investigators have reported the finding of increased lung thallium-201 at rest in patients with acute pulmonary edema after acute myocardial infarction (AMI)[8] and in other situations characterized by compromised left ventricular function or elevated left atrial pressure.[9,10] There are few data on the significance of this finding in a large group of patients with AMI, however. In a prospective study, patients admitted with suspected AMI or unstable angina underwent rest thallium-201 imaging, radionuclide ventriculography and coronary arteriography. We observed increased lung uptake of thallium-201 at rest in some patients with AMI and we describe the clinical, hemodynamic and prognostic significance of this finding.

METHODS

Ninety-six consecutive patients admitted to the coronary care unit with chest pain thought to be due to AMI or unstable angina were studied prospectively. Patients in cardiogenic shock (Killip class IV) or with terminal cardiac illness at the time of admission were not included. Women of child-bearing age were excluded, as were patients with valvular heart disease, myocarditis, cardiomyopathy or left bundle branch block. Consent was obtained from all patients and the study was approved by the hospital's ethical committee.

Study design: Patients presenting within 48 hours of the onset of chest pain were entered in the study. Rest thallium-201 imaging was carried out within 4 days of the onset of chest pain. Rest radionuclide ventriculography was performed 5 to 14 days later, and cardiac catheterization was performed 4 to 6 weeks later.

For the estimation of total serum creatine kinase and the MB fraction, venous blood samples were drawn every 6 hours for the first 36 hours and every 8 hours for the next 36 to 48 hours. Standard 12-lead electrocardiograms were obtained at the time of admission, during episodes of chest pain and daily during the hospital stay.

Thallium-201 scintigraphy: Thallium-201 was given intravenously in a dose of 74 MBq 72 to 96 hours after the onset of chest pain. Planar cardiac images were obtained in 3 standard views (anterior, 45° left anterior oblique and left lateral) starting 15 to 20 minutes after the injection. Each view was acquired over 10 minutes using a General Electric 400 AT gamma camera and a Star computer (IGE Medical Systems Ltd.). The energy window was adjusted for thallium-201 photopeak (69 to 83 keV). The data were stored in a 128 × 128 matrix for further analysis.

Radionuclide ventriculography: Red cells were labeled in vivo with 740 MBq of technetium-99m pertechnetate. Equilibrium gated blood pool ventriculography was performed in 3 standard views (anterior, 30 to 45° left anterior oblique with 5 to 10° caudal tilt to obtain best septal separation and left lateral). Twenty-four frames/cardiac cycle were obtained for a fixed count number of 5 million using an Elscint 215M mobile gamma camera (Elscint).

Coronary arteriography: Coronary arteriography was performed 4 to 6 weeks later in multiple projections. Coronary arteries with ≥50% luminal narrowing seen in at least 1 view were considered as vessels with significant disease.

TABLE I Classification of the Study Population (n = 96)

Variable	AMI (n = 62)	Unstable Angina (n = 12)	No Evidence of AMI or Resting Ischemia (n = 22)
Age (yrs)	60 ± 10	54 ± 11	55 ± 9
M:F	49:13	6:6	12:10
Diabetes mellitus	7	4	2
Systemic hypertension (>165/100 mm Hg)	19	6	7
Healed MI	18	9	5
Abnormal L-TI	20*	1	3

* p <0.02.
AMI = acute myocardial infarction; L-TI = lung thallium-201 uptake.

Data interpretation: All data were analyzed by 2 trained and blinded observers. Patients were classified into 3 groups: AMI, unstable angina and no evidence of AMI or resting ischemia, based on the results of cardiac enzymes, electrocardiograms and clinical course independent of thallium-201 results.

Thallium-201 images were interpreted semiquantitatively using a polar scoring system.[11] The left ventricular myocardium in each planar view was divided into 5 segments and each segment was scored as shown in Figure 1. The left ventricular myocardium was divided into

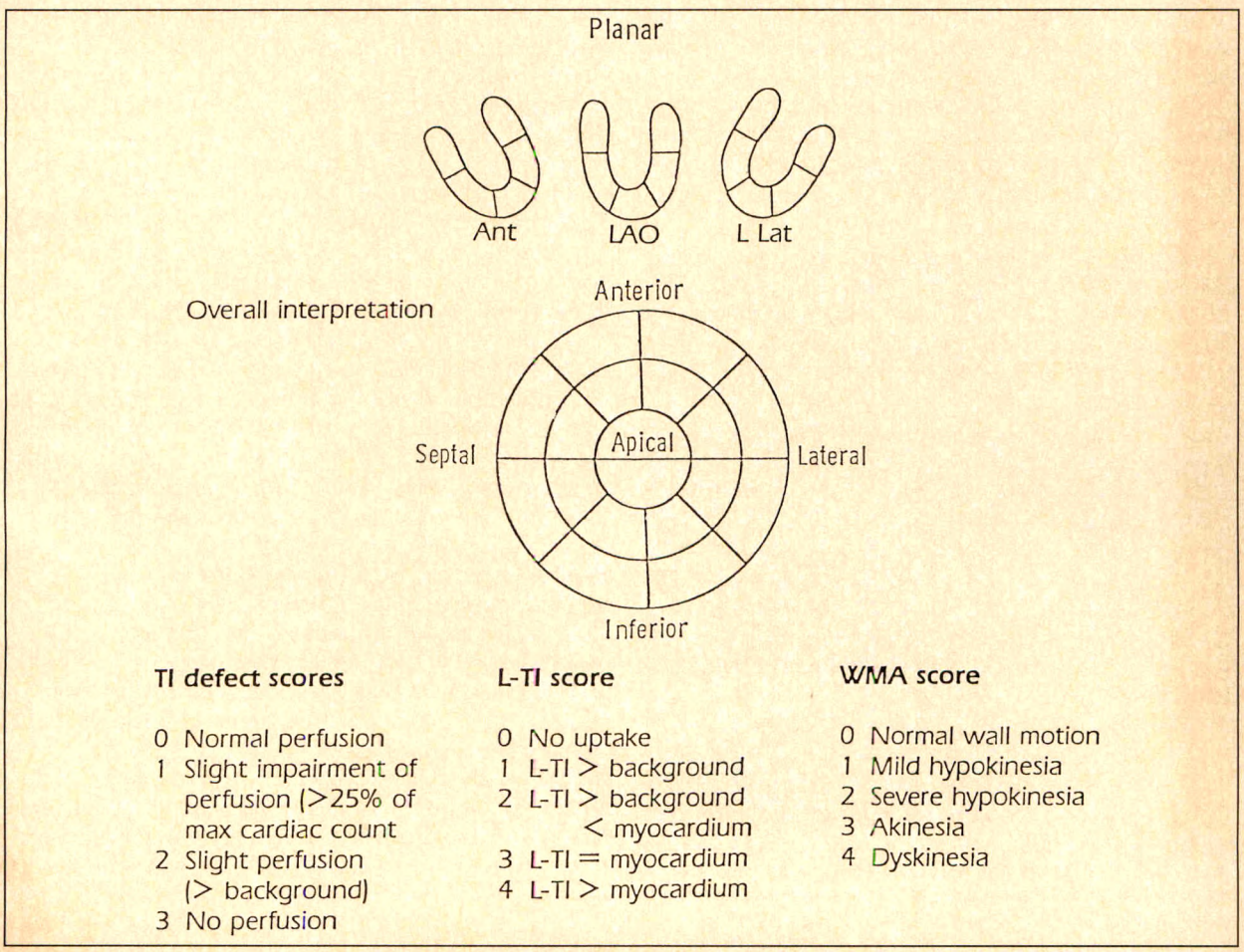


FIGURE 1. Schematic representation of the left ventricular myocardium as seen on planar views and on polar image and the scores on thallium-201 images and radionuclide ventriculography. Ant = anterior; LAO = left anterior oblique; LLat = left lateral; L-TI = lung thallium-201 uptake; TI = thallium; WMA = wall motion abnormality.

TABLE II Comparison of AMI Patients With Abnormal L-Tl With the AMI Patients Without This Finding

	L-Tl present (n = 20)	No L-Tl (n = 42)	p Value	F (discriminant analysis)
Age (yrs)	62 ± 7	59 ± 12	NS	1.04
M:F	14:6	35:7	NS	1.73
Systemic hypertension	6	13	NS	0.0
Diabetes mellitus	2	5	NS	2.26
Healed MI	5	13	NS	0.13
Thallium-201 defect score	22 ± 7	12 ± 8	<0.0001	20.07
LVEF (%)	35 ± 14	49 ± 14	<0.002	11.95
WMA score	25 ± 13	13 ± 12	<0.0001	11.66
Peak CK	2,410 ± 1,247	1,496 ± 1,228	<0.01	6.53
CE of heart failure	15	7	<0.0001	33.3
No diseased vessels	1.9 ± 0.8	1.9 ± 0.8	NS	0.03
Q-wave AMI	16	27	NS	1.3
Location of AMI				
Anterior	12	16	NS	2.73
Inferior	8	18	NS	
No ECG location	0	6	NS	
Interval between pain and Thallium-201 imaging (hrs)	82 ± 21	80 ± 29	NS	0.27
Deaths	4	1	<0.02	3.96

AMI = acute myocardial infarction; CE = clinical evidence; CK = creatine kinase; EF = ejection fraction; ECG = electrocardiographic; L-Tl = lung thallium-201 uptake; LV = left ventricular; NS = not significant; WMA = wall motion abnormality.

anterior, lateral, inferior and septal walls and apex. Each wall was further subdivided into 4 segments and the apex into 2 segments (Figure 1). The scores of individual segments were added to obtain a thallium-201 defect score.

The lung fields in the anterior view were examined for evidence of thallium-201 uptake. Abnormal lung thallium-201 uptake was considered to be present when the mediastinum appeared as a tracer-free region in contrast to the medial borders of the lungs. Lung thallium-201 uptake was graded according to increasing activity of the tracer. Grade 0 was thought to be present when the mediastinum could not be clearly delineated. Grade 1 was present when the lung activity was just above the background but the mediastinal border was clearly identified. Grade 2 was present when lung activity was clearly higher than background but less than maximal cardiac intensity. Grade 3 was present when cardiac and lung activity were equal. Finally, grade 4 was present when lung activity exceeded maximal heart activity (Figure 1). Differences in opinion were settled by input from a third experienced blinded observer and the majority opinion prevailed.

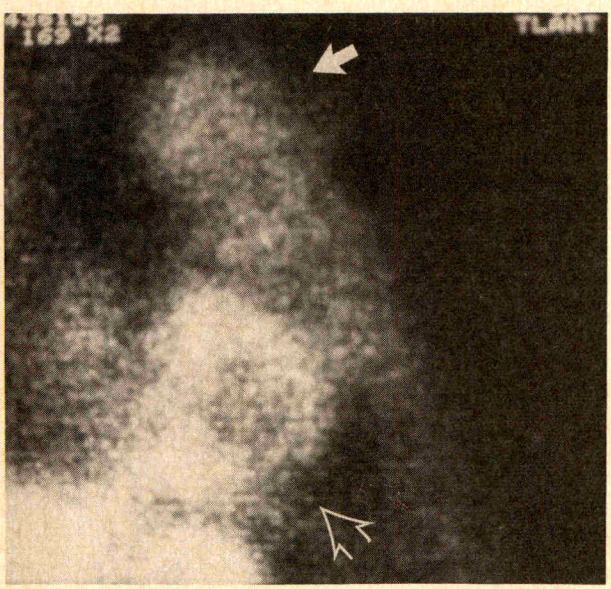


FIGURE 2. Rest thallium-201 (anterior view) of a 58-year-old man with acute inferolateral myocardial infarction and no previous myocardial infarction. The left ventricular ejection fraction was 32%; peak CK was 1,678 IU/liter. The left circumflex coronary artery was totally occluded and the left anterior descending artery had 50% narrowing. *Open arrow* indicates myocardial perfusion defect and *solid arrow* indicates abnormal lung thallium-201 uptake.

Radionuclide ventriculography was analyzed using a semiautomatic program to calculate the left ventricular ejection fraction.[12] The left ventricular myocardium was divided into 5 segments in each of the 3 views and each segment was scored for wall motion abnormality as shown in Figure 1. A total score obtained from all the segments with wall motion abnormality was designated as the wall motion abnormality score.

Patient contact was maintained for up to 9 months after the original event. Any adverse cardiac event was recorded.

Statistical analysis: All values were expressed as mean ± standard deviation. Continuous variables were each compared using Student's unpaired 2-tailed *t* test, whereas discrete variables were analyzed using the chi-square test. A p value <0.05 was considered significant. Stepwise discriminant function analysis was performed across all variables using the BMDP statistical package.[13]

RESULTS

Rest thallium-201 images were obtained in 96 patients (67 men, 29 women). Sixty-two patients had an

AMI, 12 had unstable angina and 22 had neither. Table I lists the patient characteristics in each group. Regional myocardial perfusion abnormalities were seen in 58 of 62 (94%) with AMI. Abnormal lung thallium-201 uptake was present in 24 patients; 20 of 62 patients with acute myocardial infarction (Figure 2) and 4 of 34 without acute myocardial infarction ($p < 0.02$).

Of the 4 patients with abnormal lung thallium-201 but without AMI, 1 had unstable angina, 1 had previous AMI and left ventricular aneurysm, 1 had accelerated systemic hypertension and hypertensive heart failure and 1 had no evidence of obstructive coronary artery or pulmonary disease. Table II lists a comparison between the patients with AMI and abnormal lung thallium-201 uptake and those with AMI without lung thallium-201 uptake. Age, sex, incidence of hypertension, diabetes and prevalence of healed myocardial infarction did not differ in the 2 groups. However, there were significant differences when thallium-201 defect scores, wall motion abnormality scores, ejection fraction, peak creatine kinase levels and incidence of heart failure were compared (Table II, Figures 3 and 4).

In the group with increased lung thallium-201 uptake, the segmental thallium-201 defect score was higher (22 ± 7 vs 12 ± 8, $p < 0.001$). None of the 4 patients with AMI without segmental thallium-201 abnormality had an increased lung thallium-201 activity. The patients with abnormal lung thallium-201 uptake had greater impairment of left ventricular ejection fraction (34 ± 14 vs $49 \pm 14\%$, $p < 0.002$). Wall motion abnormality score was also higher in the patients with abnormal lung tracer uptake (25 ± 13 vs 13 ± 12, $p < 0.001$). The peak creatine kinase levels were higher in the group with increased lung thallium-201 uptake ($2,410 \pm 1,247$ vs $1,496 \pm 1,228$ IU/liter; $p < 0.01$) (normal range 20 to 205). A higher percentage of the patients with increased lung thallium-201 uptake had clinical evidence of left ventricular failure (75 vs 17%, $p < 0.0001$) during the hospital stay.

Coronary angiography was performed in 17 of 20 patients with AMI and abnormal lung thallium-201 and in 37 of 42 with AMI but with no pulmonary thallium-201 uptake. All but 1 patient in the latter group had significant obstructive coronary artery disease. However, there were no differences between the mean number of the coronary arteries with significant disease in the 2 groups of patients (1.94 ± 0.83 vs 1.91 ± 0.82, difference not significant).

The time interval between the onset of chest pain and thallium-201 imaging did not differ in the patients

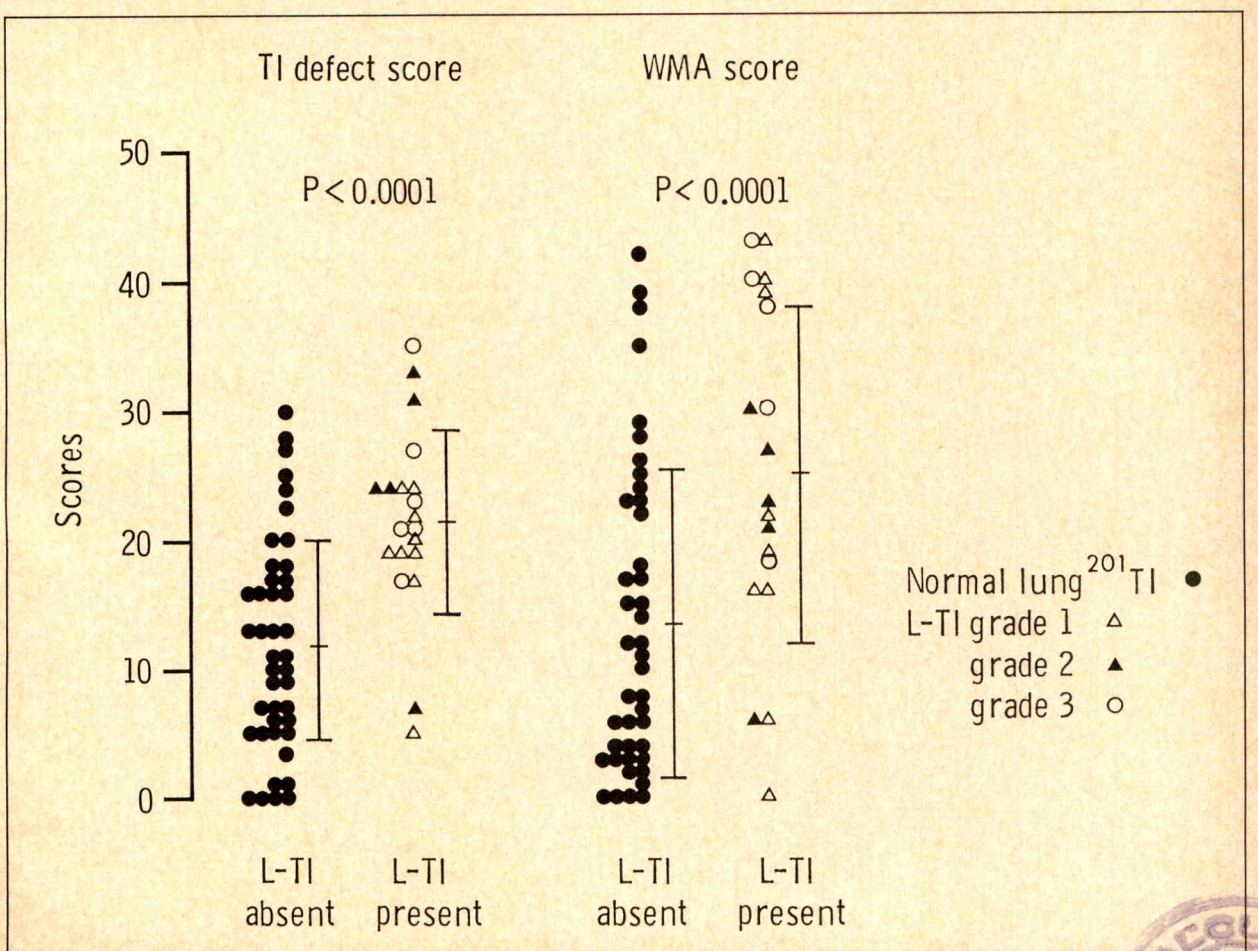


FIGURE 3. Comparison of the thallium-201 defect scores and wall motion abnormality scores between the group of patients with acute myocardial infarction and lung thallium-201 uptake and the group with acute myocardial infarction and no lung thallium-201 uptake. Abbreviations as in Figure 1.

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with AMI and abnormal lung thallium-201 uptake compared to those with AMI but without lung thallium-201 uptake (82 ± 21 vs 80 ± 29 hours, difference not significant).

Of the 20 patients with abnormal lung uptake of thallium-201, 5 (25%) had grade 3 uptake, 5 (25%) had grade 2 uptake and 9 (45%) had grade 1 uptake. None had grade 4 uptake. All 5 patients with grade 3 lung uptake had overt left ventricular failure and had lower ejection fractions compared to those with grade 1 uptake. The small numbers did not permit subgroup analysis, but the degree of rest lung thallium-201 uptake corresponded with the underlying severity of left ventricular dysfunction.

Stepwise discriminant function analysis showed heart failure to be the most important determinant of abnormal lung thallium-201 uptake. The F values in Table II show the relative importance of the parameters. When the clinical variables were excluded, thallium-201 defect score emerged as the most important correlate of abnormal lung thallium-201 uptake.

During the short-term follow-up (to 9 months), there were 6 deaths among the 95 patients, and all were of cardiac origin. One patient in the noninfarction group was lost to follow-up. Five deaths occurred in the patients with acute infarction and 1 in the unstable angina group. Four of 5 deaths in the AMI group occurred in the patients with abnormal lung thallium-201 uptake, compared to only 1 in the group without lung thallium-201 uptake ($p < 0.02$). One patient with unstable angina, who died 1 week after the investigation, also had increased lung thallium-201 uptake.

DISCUSSION

Increased lung uptake of thallium-201 during exercise is usually observed in patients with severe myocardial ischemia or those with impaired left ventricular function. Boucher et al[1] first described this phenomenon. Bingham et al[3] showed that lung thallium-201 extraction is increased by elevation in left atrial pressure or by prolongation of pulmonary transit time and concluded that exercise-induced left ventricular failure was the likely cause.[3] In patients with coronary artery disease, lung thallium-201 uptake during exercise was closely correlated to the severity of underlying coronary artery disease,[1,2,14,15] extent of reversible ischemia[14,15] and resting left ventricular ejection fraction.[4–6,15]

The finding of increased lung thallium-201 uptake at rest has been previously reported in patients with various forms of cardiac disease.[9,10] Appearance and distri-

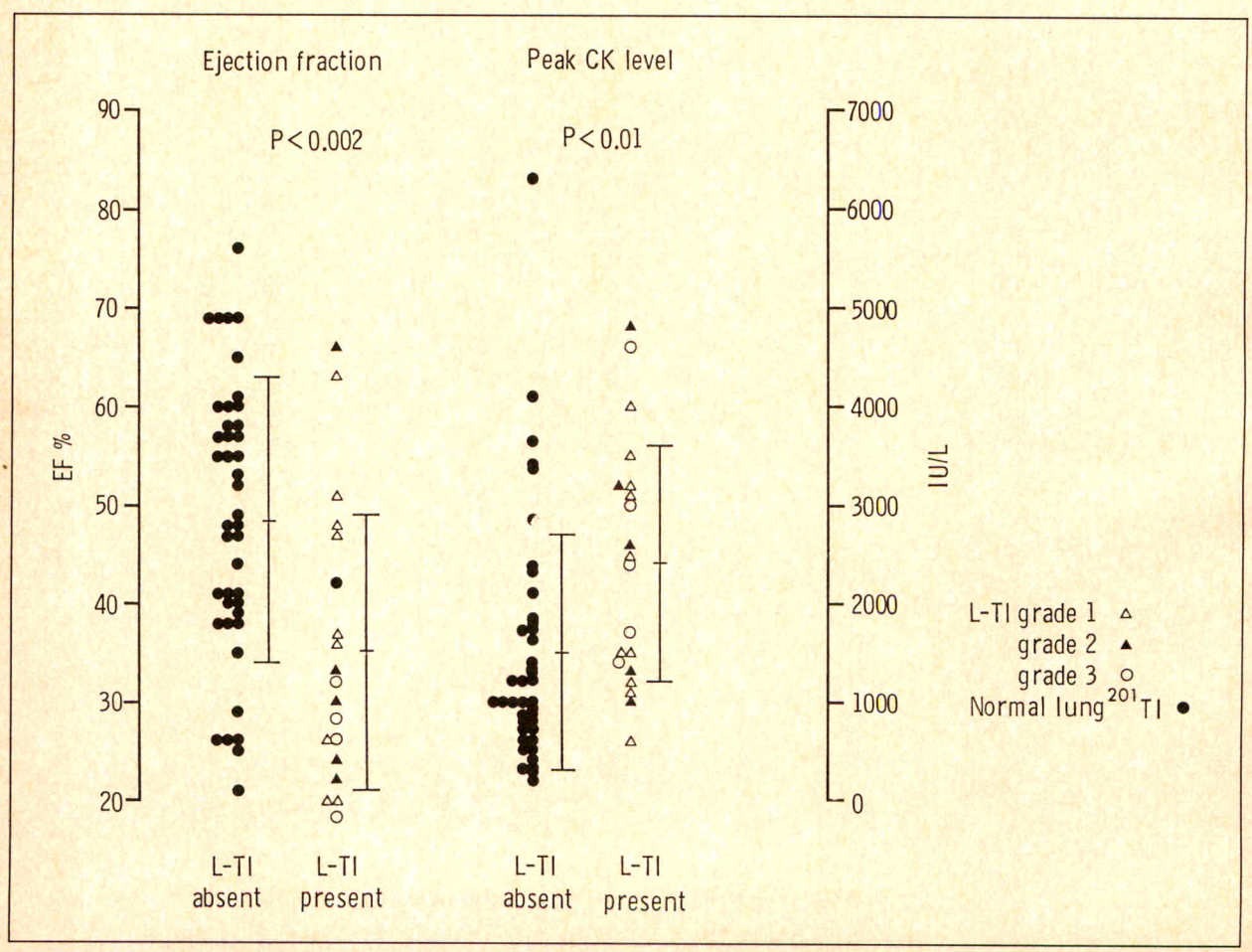


FIGURE 4. Comparison of the ejection fraction and peak creatine kinase (CK) levels between the group of patients with acute myocardial infarction and lung thallium-201 uptake, and the group with acute myocardial infarction and no lung thallium-201 uptake. Abbreviations as in Figure 1.

bution of frank radiologic pulmonary edema in acute myocardial infarction has also been correlated with lung thallium-201 uptake at rest.[8] However, Fazio et al[16] have demonstrated that increased lung water may not always be detected with a standard chest radiograph. Previous studies have shown that thallium-201 inhaled in an aerosol enters the systemic circulation in a normal subject,[17] thus suggesting a free movement of the tracer across the alveolar-capillary bed. Furthermore, when thallium-201 was injected intravenously in an animal with toxic chemical pulmonary edema, thallium-201 was found to accumulate in the edema fluid.[17] These data suggest that thallium-201 uptake by the lung may be indicative of pulmonary edema.

In our study, lung thallium-201 uptake at rest in patients with AMI was associated with larger infarct size, greater degree of left ventricular dysfunction, higher incidence of left ventricular failure and higher mortality. In patients without AMI, abnormal lung thallium-201 uptake was noted in those with left ventricular dysfunction due to previous AMI, unstable angina or accelerated hypertension. Only 1 of 24 (4%) patients with abnormal lung thallium-201 uptake had insignificant coronary artery disease. In this study, thallium-201 imaging was carried out at rest during the acute phase of myocardial infarction. Abnormal lung thallium-201 uptake was present in 32% of the patients with AMI, even though imaging was performed 72 hours after the onset of chest pain. On stepwise discriminant analysis we observed the presence of heart failure to be the most important determinant of abnormal lung thallium-201 uptake. When clinical parameters were removed, thallium-201 defect score was the most important correlate, thereby indicating a direct correlation with the extent of perfusion abnormality.

We used semiquantitative visual assessment of the lung fields for abnormal lung thallium-201 uptake, rather than using a count-based quantitative method. Because the distribution of thallium-201 in lung fields is not uniform, we thought a visual scoring of the entire lung fields may be more accurate than the quantitative methods using only fixed regions of interest from the lung fields.

Our results indicate that the examination of the lung fields for abnormal thallium-201 uptake may add considerably to the information derived from rest thallium-201 imaging in patients with AMI. In addition to providing information regarding the location and extent of myocardial infarction, lung thallium-201 analysis may provide additional information relating to left ventricular dysfunction and prognosis. With the wider application of AMI-limiting interventions, rest thallium-201 imaging may provide important parameters for the noninvasive assessment of these interventions.

Acknowledgment: We gratefully acknowledge the help of Mradula Ravat and Aasiah Rahim in the preparation of this manuscript.

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Ability of Dipyridamole–Thallium-201 Imaging One to Four Days After Acute Myocardial Infarction to Predict In-Hospital and Late Recurrent Myocardial Ischemic Events

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The ability of dipyridamole–thallium-201 imaging to predict in-hospital and late cardiac events when performed very early (62 ± 21 hours, range 23 to 102) after acute myocardial infarction (AMI) was tested in 50 patients. During hospitalization, 1 patient developed recurrent AMI and 8 patients developed recurrent angina after MI associated with ST-segment depression at 60 ± 42 hours after the dipyridamole–thallium-201 imaging; of these, 6 required urgent coronary revascularization. No patient died in-hospital. There were no serious adverse effects during the dipyridamole protocol. Using stepwise multivariate logistic regression analysis, the best and only statistically significant predictor of in-hospital ischemic cardiac events was the presence of thallium-201 redistribution within the infarct zone ($p = 0.0001$). Of 20 patients with infarct zone thallium-201 redistribution, 9 (45%) developed in-hospital ischemic cardiac events compared to 0 of 30 patients without infarct zone thallium-201 redistribution ($p < 0.0001$). During a follow-up 12 ± 7 months after discharge, 3 additional patients with infarct zone thallium-201 redistribution developed recurrent AMI or unstable angina, whereas no patient without infarct zone thallium-201 redistribution developed ischemic cardiac events. These data suggest that dipyridamole–thallium-201 imaging performed very early after AMI may identify a subgroup of patients at high risk for in-hospital and late ischemic cardiac events. Such patients may benefit from early cardiac catheterization and revascularization. Patients without infarct zone thallium-201 redistribution appear to be at very low risk for in-hospital and late ischemic cardiac events and may be candidates for early discharge.

(Am J Cardiol 1990;65:160–167)

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Several features of dipyridamole–thallium-201 myocardial perfusion imaging suggest that this technique has the potential to play an important role in the early management of acute myocardial infarction (AMI). First, the ability of thallium-201 imaging in general to distinguish residual jeopardized viable myocardium from infarcted myocardium[1–3] may allow identification of patients with spontaneous or pharmacologically induced reperfusion and "incomplete" infarctions who may be at high risk for early, in-hospital cardiac events.[4–8] Second, thallium-201 imaging has been shown to have significant prognostic value in patients with a wide range of coronary artery disease.[9–13] This suggests the possibility that thallium-201 imaging could be used very early after AMI to distinguish between high-risk patients most likely to benefit from additional early diagnostic or therapeutic interventions and low-risk patients whose hospitalization might be safely shortened. Third, thallium-201 imaging with dipyridamole-induced coronary vasodilation only modestly increases determinants of myocardial oxygen demand,[2,14,15] but provides superior quality images and increased sensitivity for detecting residual critical coronary lesions compared to resting studies[2,14,16–18] and can reveal myocardial ischemia not detected on a submaximal exercise thallium-201 study.[19] Thus, the technique is especially well suited for patients with recent AMI. The present study was therefore designed to determine whether dipyridamole–thallium-201 myocardial imaging, performed very early (1 to 4 days) after AMI, could predict in-hospital and late ischemic cardiac events.

METHODS

Patient population: All patients admitted or transferred to the Medical Center Hospital of Vermont within 72 hours of AMI, and thus available for dipyridamole–thallium-201 imaging at approximately 24 to 96 hours after myocardial infarction, were considered for the protocol. Patients whose clinical status already identified them as high-risk were excluded: recurrent angina after myocardial infarction, cardiogenic shock or Forrester class IV hemodynamics,[20] and resting systolic blood pressure <90 mm Hg. Other exclusions included bronchospasm requiring theophylline, or unavailability of thallium-201, technician or camera precluding imaging during the approximate 24- to 96-hour interval after onset of AMI.

From May 5, 1986, through July 26, 1988, 657 patients were admitted within 72 hours of AMI. Of these,

191 patients were excluded because of the outlined clinical criteria. An additional 10 patients were excluded because of theophylline use. Of the remaining 466 who were eligible, 50 entered the study. The remainder were not successfully recruited because of unavailability of a scintillation camera, technician or thallium-201 within the 24- to 96-hour interval after myocardial infarction, or patient refusal. Clinical characteristics of the study cohort and eligible nonenrolled group are listed in Table I. Antecedent chest pain was present in 17 (34%) patients in the study cohort; 3 (6%) had evidence of congestive heart failure at the time of study. There was no significant difference in any characteristic between the study cohort and the rest of the eligible group (Table I). Dipyridamole–thallium-201 imaging was performed 62 ± 21 hours (range 23 to 102 hours) after AMI.

Dipyridamole–thallium-201 protocol and thallium-201 image acquisition: All studies were performed in the cardiac intensive care unit using a standard portable, small field-of-view Anger camera (Technicare 420). Patients were monitored continuously with an intraarterial line when available (4 patients), or with sphygmomanometry (46 patients) performed by the physician supervising the study. Cardiac rhythm and heart rate were continuously monitored by oscilloscope. Baseline heart rate and blood pressure were obtained in duplicate 10 minutes apart before infusion. A 12-lead electrocardiogram, heart rate and blood pressure were then recorded every minute for the first 20 minutes of the study and every 10 minutes for the next 40 minutes. A standard dipyridamole infusion protocol[15] was used. Patients were kept supine throughout the protocol to minimize hypotension. Imaging was begun 5 minutes after thallium-201 injection. Standard 8-minute 40° left anterior oblique, anterior and 90° left lateral collections were acquired initially and repeated in the same sequence 2 to 4 hours later.

Theophylline was administered intravenously in patients who developed significant electrocardiographic changes (≥1 mm of horizontal or downsloping ST-segment depression) or ischemic symptoms that did not spontaneously resolve. No patient required theophylline before the onset of thallium-201 imaging. The initial theophylline dose was 50 to 100 mg and was repeated every 2 to 3 minutes until resolution of symptoms or ST depression.

Thallium-201 image analysis: Images were analyzed quantitatively using a method previously described and validated at this institution.[21] Briefly, the heart was divided into septal, inferior-apical and posterior segments in the left anterior oblique projection and anterior, apical and inferior segments in the anterior and lateral projections. All perfusion defects were defined either as fixed or as showing significant redistribution.[21] When correlated with available coronary angiographic data the anterior and septal segments were assumed to be supplied by the left anterior descending artery, the inferior segments by the right coronary artery and the posterior wall by the left circumflex artery.

All thallium-201 perfusion defects were classified as being within the infarct zone or outside the infarct zone, based on the relation between the thallium-201 myocardial segment involved and the site of the Q-wave infarction. Among the 3 patients with non-Q-wave infarction, 1 patient had 1-vessel disease with occlusion of the left anterior descending artery at coronary angiography and an anteroapical perfusion defect that was assumed to be within the infarct zone. The 2 other patients with non-Q-wave infarction had perfusion defects involving 2 different coronary vascular territories, each with significant redistribution (and no fixed defects). These patients were assumed to have perfusion defects both within and outside of the infarct zone.

TABLE I Comparison of Clinical Variables in Study Cohort Versus Eligible Nonenrolled Population

Variable	Study Cohort (n = 50)	Eligible Nonenrolled Population (n = 416)	p Value
Age (yrs)	57 ± 11	58 ± 14	NS
Sex (M/F)	42/8	324/92	NS
Prior MI (%)	6 (12)	87 (21)	NS
Acute anterior MI (%)	19 (38)	165 (40)	NS
Acute non-Q-wave MI (%)	3 (6)	58 (14)	NS
Thrombolytic therapy (%)	25 (50)	162 (39)	NS

MI = myocardial infarction; NS = not significant.

TABLE II Comparison of Clinical Variables in Catheterization Cohort Versus Noncatheterization Cohort

Variable	Cardiac Catheterization Cohort (n = 34)	Noncardiac Catheterization Cohort (n = 16)	p Value
Age (yrs)	55 ± 10	60 ± 13	NS
Sex (M/F)	31/3	11/5	NS
Prior MI (%)	5 (15)	1 (6)	NS
Acute anterior MI (%)	15 (44)	4 (25)	NS
Acute non-Q-wave MI (%)	2 (6)	1 (6)	NS
Thrombolytic therapy (%)	21 (62)	4 (25)	<0.05

Abbreviations as in Table I.

Cardiac catheterization: Cardiac catheterization was performed in 34 patients using standard techniques at 4.4 ± 2.5 days after infarction. All decisions for performing catheterization were made by the treating physician. There was no significant difference in age, sex, prior myocardial infarction, frequency of anterior infarction or non-Q-wave infarction among catheterized compared to noncatheterized study patients (Table II). However, those undergoing catheterization had more frequently received thrombolytic therapy (62%) than patients who did not undergo catheterization (25%) (Table II). Significant coronary stenosis was defined as a luminal diameter narrowing of ≥50% in either the main epicardial artery or a major branch. Collateral vessels were graded as absent, poor (faint contralateral filling of a minor branch) or good (dense contralateral filling of a major artery or branch). The infarct vessel was defined as the left anterior descending artery for anterior infarctions, the right coronary artery for inferior myocardial infarctions and the left circumflex artery for posterior infarction. Two patients with non-Q-wave

TABLE III Characteristics of Patients Developing In-Hospital Ischemic Cardiac Event

				Catheterization Data				Dipyridamole–Tl-201 Imaging					
Patient	Age (yrs)	MI Site	Thrombo-lytic Drugs	Infarct Vessel % Stenosis	Infarct Zone Wall Motion	Good Collateral Vessels	MVD	Chest Pain	ST↓	Infarct Zone Redistri-bution	Event	Hours After Tl-201	Course
1	49	A	0	100	Akinetic	+	0	+	+	+	Angina, ST↓	34	Bypass
2	66	A	+	85	Mild HK	0	+	0	0	+	Angina, ST↓	8	Bypass
3	59	I	+	90	Akinetic	0	+	+	0	+	Angina, ST↓	51	Bypass
4	48	I	0	100	Mild HK	+	0	+	0	+	Angina, ST↓	96	Medical Rx
5	58	I	0	95	Mod HK	0	+	0	+	+	Angina, ST↓	36	Bypass
6	62	I	0	90	Severe HK	0	+	+	0	+	MI	120	Bypass
7	73	A	0	100	Severe HK	+	0	0	+	+	Angina, ST↓	24	Medical Rx
8	71	A	0	100	Severe HK	+	+	0	0	+	Angina, ST↓	120	Bypass
9	50	A	+	90	Mild HK	0	+	0	0	+	Angina, ST↓	48	Medical Rx

A = anterior; I = inferior; HK = hypokinesis; MI= myocardial infarction; mod = moderate; MVD = multivessel coronary disease; NQ = non-Q-wave; Rx = treatment; ST↓ = ST-segment depression; Tl = thallium.

infarctions underwent cardiac catheterization. One had 1-vessel left anterior descending artery occlusion that was presumed to be the infarct vessel. The other had multivessel disease but only the right coronary artery was completely occluded and, for the purpose of analysis, was assumed to be the infarct vessel. Biplane left ventriculograms were performed and were divided into anterior, apical and inferior walls on the right anterior oblique projection and septal, inferoapical and posterior walls on the left anterior oblique projection. Wall motion within the infarct zone, as defined by the location of electrocardiographic Q waves, was categorized as good (normal, mild-to-moderate hypokinesis) or poor (severe hypokinesis, akinesis, dyskinesis). For the 2 patients with non-Q-wave infarction, the infarct zone was designated as the area supplied by the infarct vessel as already defined.

Follow-up data: Each patient's clinical course was followed daily after the dipyridamole–thallium-201 study until discharge from the hospital. The mean hospital stay was 10 ± 3 days. Ischemic cardiac events were defined as development of recurrent angina pecto-

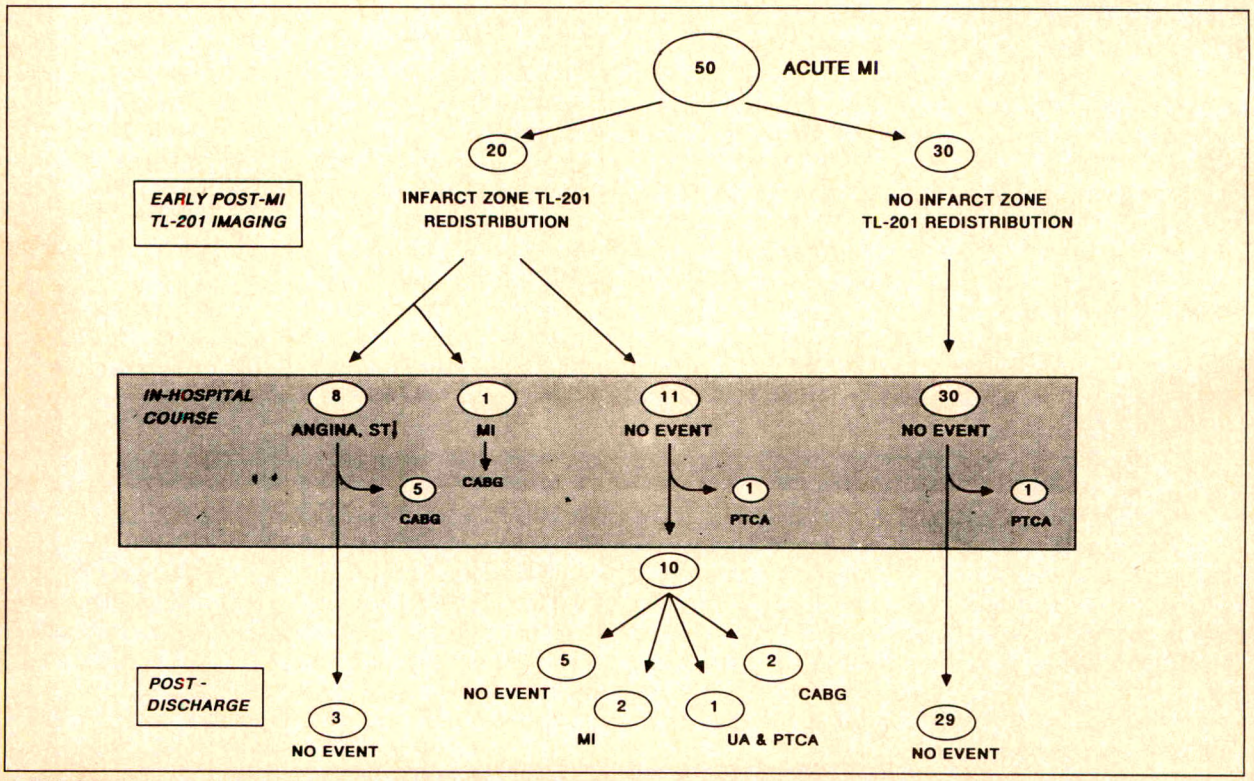


FIGURE 1. Outcome in-hospital and after discharge of patients based on the presence or absence of infarct zone thallium-201 redistribution seen on early postmyocardial infarction imaging. CABG = coronary artery bypass graft surgery; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; ST ↓ = ST-segment depression; TL = thallium; UA = unstable angina.

TABLE IV Univariate Comparison of Patient Variables According to Ischemic In-Hospital Cardiac Event Outcome

	Patients Without Ischemic Cardiac Events (n = 41)	Patients With Ischemic Cardiac Events (n = 9)	p Value
Clinical variables			
Age	56 ± 12	60 ± 9	0.41
Sex (M:F)	36:5 (88:12)	6:3 (67:33)	0.12
Nitrate	31 (76)	6 (67)	0.58
β blocker	16 (39)	3 (33)	0.75
Calcium antagonist	25 (61)	4 (44)	0.36
Thrombolytic treatment	22 (54)	3 (33)	0.27
MI site (A:I:P:NQ)	13 (32):25 (61):1 (2):2 (5)	6 (67):2 (22):0:1 (11)	0.16
Peak serum CK level	1,348 ± 1,371	959 ± 709	0.41
Dipyridamole protocol variables			
Chest pain	16 (39)	4 (44)	0.76
ST depression	10 (24)	3 (33)	0.58
HR rest	76 ± 11	81 ± 12	0.20
Peak	89 ± 12	95 ± 12	0.22
BP systolic rest	115 ± 12	118 ± 21	0.56
Nadir	105 ± 13	104 ± 14	0.84
HR × BP systolic rest	8,741 ± 1611	9,633 ± 2,345	0.17
Peak	10,107 ± 1941	10,863 ± 2,570	0.32
Catheterization variables (n = 30)			
Infarct vessel % stenosis	85 ± 18	94 ± 6	0.03
Good collateral vessels	6/25 (24)	3/9 (33)	0.59
Good infarct zone wall motion	9/25 (35)	3/9 (33)	0.79
Multivessel coronary disease	11/25 (44)	6/9 (67)	0.29
Ejection fraction	55 ± 7	49 ± 10	0.08
Tl-201 imaging variables			
Infarct zone Tl-201 redistribution	11 (27)	9 (100)	0.0001
Noninfarct zone Tl-201 redistribution	2 (6)	4 (44)	0.004

Values in parentheses are percents.
Abbreviations as in Table III.

ris, myocardial infarction or cardiovascular death. Coronary revascularization with coronary angioplasty or bypass surgery was also noted, but these were not considered ischemic events if they did not occur in response to development of recurrent angina or infarction. Management decisions were not made on the basis of thallium-201 imaging results because these were not made available to the patients' treating physicians.

Follow-up after discharge was obtained by telephone interviews of each patient and by examination of their physicians' office notes and hospital records, and was 100% complete.

Statistical analysis: Values are presented as mean ± standard deviation. Maximal changes in mean heart rate, blood pressure and rate-pressure product after dipyridamole were analyzed using a paired *t* test. Frequency comparisons were performed using chi-square analysis or Fisher exact test, when appropriate. To examine the univariate relation of each variable to in-hospital ischemic cardiac events, a Pearson chi-square was used for categorical variables and a *t* test for continuous variables. A significance level of $p < 0.05$ was used. To determine the relative prognostic value of each variable, stepwise multivariate logistic regression was used (BMDPLR, revised 1987).

RESULTS

Hemodynamic effects of dipyridamole: Heart rate increased modestly after dipyridamole, increasing from a mean of 77 ± 11 to 89 ± 13 beats/min ($p < 0.01$) and reaching a peak at 7 ± 3 minutes after initiation of infusion. Systolic and diastolic blood pressure decreased, from 116 ± 12 to 105 ± 13 mm Hg ($p < 0.001$), and from 68 ± 10 to 62 ± 9 mm Hg ($p < 0.001$), respectively, also reaching a nadir at 7 ± 3 minutes after initiation of infusion. Maximal heart rate × systolic pressure product increased from 8,901 ± 2,085 to a peak of 10,243 ± 2,047 beats/min × mm Hg ($p < 0.001$) at 8 ± 4 minutes after initiation of infusion. This returned to baseline at 15 ± 7 minutes.

Adverse effects: No recurrent infarctions, serious arrhythmias, cardiac arrests or deaths were observed during any dipyridamole–thallium-201 protocol. Chest pain, significant ST-segment depression or both developed in 23 of 50 (46%) patients during the procedure; 19 required theophylline (88 ± 46 mg, range 50 to 200). All ischemic symptoms or ST-segment depressions were reversed within 3 to 4 minutes and no adverse effects occurred from theophylline infusion. In response to theophylline, there was a significant decrease in heart rate (89 ± 9 to 78 ± 9 beats/min, $p < 0.0001$) and rate-pressure product (11,230 ± 1,622 to 9,397 ± 1,447 beats/min × mm Hg, $p < 0.0001$) as ischemia was relieved.

Minor side effects of dipyridamole included mild headache (13 of 50) and mild nausea (2 of 50). One patient with headache and nausea was given 50 mg theophylline with rapid resolution of symptoms.

Thallium-201 imaging results: Thallium-201 perfusion defects within the infarct zone were seen in all 50

TABLE V Multivariate Predictors of Ischemic In-Hospital Cardiac Events

Variable	Step 0, Before Predictors Entered Into Logistic Regression Model		Step 1, After Infarct Zone Tl-201 Redistribution Entered Into Model	
	Chi-Square	p Value	Chi-Square	p Value
Infarct zone Tl-201 redistribution	19.61	0.00001	(19.61)	(0.00001)
Noninfarct zone redistribution	6.78	0.009	1.64	0.20
Patient gender	2.10	0.15	0.61	0.44
Myocardial infarction location	5.36*	0.16	1.87*	0.60
Thrombolytic therapy	1.24	0.27	0.31	0.58
Peak creatine kinase level	0.83	0.36	1.68	0.19
Calcium antagonist use	0.82	0.37	0.00	0.96
Age (yrs)	0.69	0.40	0.10	0.75
Nitrate use	0.29	0.59	0.02	0.89
Dipyridamole-induced ST	0.29	0.59	0.09	0.77
β-blocker use	0.10	0.75	0.02	0.89
Dipyridamole-induced chest pain	0.09	0.76	0.00	0.96
Ejection fraction†	3.12	0.08	3.57	0.06
Infarct vessel percent stenosis†	3.02	0.08	2.66	0.10
Multivessel coronary disease†	0.46	0.50	1.63	0.20
Good collaterals to infarct vessel†	0.29	0.59	0.53	0.46
Infarct zone wall motion†	0.05	0.82	2.42	0.12

* 3 degrees of freedom; all other variables have 1 degree of freedom.
† Only patients undergoing cardiac catheterization (n = 34).
Tl = thallium.

patients. Significant thallium-201 redistribution within the infarct zone was present in 20 of 50 (40%) patients. Perfusion defects outside the infarct zone were observed in 9 patients, of whom 6 showed significant redistribution. The frequency of infarct zone thallium-201 redistribution in patients receiving thrombolytic therapy (10 of 25, 40%) was identical to the frequency in patients who did not receive thrombolytic treatment (10 of 25, 40%).

Predictors of in-hospital ischemic cardiac events: In-hospital ischemic cardiac events occurred in 9 (18%) patients, at a mean of 60 ± 42 hours after imaging and 113 ± 37 hours after infarction (Table III, Figure 1). Recurrent AMI occurred in 1 patient in the same zone as the original infarction and corresponded to an area that had shown infarct zone thallium-201 redistribution. The other 8 in-hospital ischemic cardiac events were recurrent angina after infarction associated with ST-segment depression. Six of 9 patients underwent emergency coronary bypass surgery in response to the recurrent ischemic event. The other 3 patients were managed medically. No patient died during hospitalization. Two other patients underwent coronary revascularization with angioplasty at 83 and 46 hours after thallium-201 imaging, respectively, although they did not develop antecedent recurrent ischemia or infarction (Figure 1). These were not considered in-hospital ischemic cardiac events, but were considered separately.

By univariate analysis, only thallium-201 redistribution within the infarct zone, thallium-201 redistribution outside the infarct zone and percent stenosis of the infarct vessel were significantly related to in-hospital cardiac events (Table IV). Using stepwise multivariate logistic regression analysis, the most important and only significant predictor of in-hospital ischemic cardiac events was thallium-201 redistribution within the infarct zone ($p = 0.00001$, Table V). After this variable was entered in the logistic regression model, no other variable had any additional significant prognostic value for in-hospital cardiac events.

Nine of the 20 (45%) patients with significant thallium-201 redistribution within the infarct had in-hospital cardiac events compared to 0 of 30 patients without infarct zone thallium-201 redistribution ($p < 0.0001$). The sensitivity, specificity, positive and negative predictive values of infarct zone thallium-201 redistribution for in-hospital cardiac events were 100, 73, 45 and 100%, respectively.

Among the 34 patients who had cardiac catheterization data, infarct zone thallium-201 redistribution remained the most important multivariate predictor of in-hospital ischemic cardiac events ($p = 0.00001$, Table V). After this variable was entered into the logistic regression model, no other patient variable had any additional prognostic value.

Finally, when multivariate logistic regression analysis was repeated after excluding the 2 patients who underwent coronary revascularization before discharge without recurrent in-hospital ischemic cardiac events (1 had infarct zone thallium-201 redistribution), the results were unchanged for the overall cohort as well as the subgroup undergoing cardiac catheterization.

In-hospital expenses: Although patients with infarct zone thallium-201 redistribution had somewhat longer hospital stays (12 ± 6 vs 10 ± 3 days), more total hospital charges ($13,997 ± 8,716 vs $9,263 ± 5,265) and higher average daily hospital charges ($1,087 ± 385 vs $968 ± 285) compared to patients without infarct zone redistribution, the differences were not statistically significant.

Postdischarge follow-up: Patients were followed for a mean of 12 ± 7 months (range 2 to 24 months) after

discharge. Recurrent late ischemic cardiac events included 2 patients with nonfatal AMI (both non-Q-wave) and 1 patient with recurrent unstable angina requiring emergency coronary angioplasty. Two of these events occurred within 1 month of discharge. In addition, 2 patients underwent elective coronary bypass surgery without antecedent ischemic cardiac events within 2 months of discharge. Each of these 5 patients had infarct zone thallium-201 redistribution on the dipyridamole–thallium-201 study early after infarction. Of the original group of 20 patients with infarct zone thallium-201 redistribution, 12 (60%) developed either early or late ischemic cardiac events compared to 0 of 30 patients without infarct zone thallium-201 redistribution ($p < 0.0001$) (Figure 1).

Coronary angiography correlates: A patent infarct vessel was not predicted by the presence of thallium-201 redistribution within the infarct zone. A patent infarct vessel was present in 11 of 16 (69%) patients with infarct zone thallium-201 redistribution undergoing coronary angiography compared to 10 of 18 (55%) patients without infarct zone thallium-201 redistribution ($p = 0.40$). Good angiographic collaterals were present in 4 of the 5 patients with infarct zone thallium-201 redistribution and occluded infarct vessels. The other had faint angiographic collaterals.

DISCUSSION

Our study demonstrates that dipyridamole–thallium-201 imaging performed 1 to 4 days after myocardial infarction may be useful in predicting the development of subsequent ischemic cardiac events in-hospital and after discharge in a population of clinically stable patients. Among patients with thallium-201 redistribution within the infarct zone, 45% subsequently developed recurrent ischemic cardiac events during hospitalization, most of whom required urgent revascularization. An additional 15% experienced late ischemic cardiac events. Such patients may benefit from an aggressive clinical approach, including early cardiac catheterization and revascularization, although at least some patients appeared to do well after discharge with medical treatment. Although only 1 of the 9 in-hospital cardiac events was a "hard" endpoint (recurrent myocardial infarction), risk stratification earlier than the usual study 7 to 10 days after infarction may still have advantages. Earlier identification of high-risk patients may allow scheduling *elective* cardiac catheterization, revascularization or both, which may reduce the morbidity and mortality risks of each procedure. In addition, performing earlier elective diagnostic and therapeutic interventions may result in cost savings by shortening the average hospitalization time.

Early risk stratification may have particular economic impact among the 60% of patients without infarct zone redistribution who appear to be at very low risk for cardiac events both in-hospital and after discharge. In our study cohort, the average daily hospital charge was approximately $1,000. At our hospital, dipyridamole–thallium-201 imaging costs $534. Whereas average hospital charges toward the end of the hospitalization would be somewhat less than the overall average (which included the more expensive coronary care unit charges), if patients could be safely discharged 3 or 4 days earlier than the current practice, considerable cost savings could be appreciated.

Ischemic in-hospital cardiac events: Among all patient variables, infarct zone thallium-201 redistribution was the best and only significant predictor of in-hospital ischemic cardiac events. This remained true among the subset of patients who had cardiac catheterization data available. These findings are consistent with a large body of prior investigations demonstrating the prognostic value of thallium-201 redistribution in patients presenting with chest pain,[9] or undergoing risk stratification at 10 to 14 days after myocardial infarction[10,11] or before vascular surgery.[12,13] The prognostic value is presumably related to the ability of thallium-201 redistribution imaging to identify the presence of jeopardized *viable* myocardium.[1–3]

Angiographic variables were not significant predictors of in-hospital ischemic cardiac events. Although the infarct vessel percent stenosis was greater in patients who developed ischemic cardiac events than in those who did not (Table I), there was considerable overlap. Thus, it appears that the presence of jeopardized viable myocardium in the infarct zone (based on thallium-201 imaging), regardless of underlying coronary anatomy, may be the most important predictor of in-hospital ischemic cardiac events after an AMI.

Thrombolysis: In our study group, treatment with a thrombolytic agent was not significantly related to either infarct zone thallium-201 redistribution or in-hospital ischemic cardiac events. This is somewhat surprising because successful thrombolytic treatment might be expected to be associated with a higher incidence of residual jeopardized viable myocardium in the infarct zone and hence more subsequent cardiac events. It is likely that our selection criteria excluded some patients who received thrombolytic treatment and did have "salvaged" myocardium at risk but had recurrent ischemic events before recruitment into our study.

Safety of dipyridamole early after infarction: No patient developed AMI, serious arrhythmia, cardiac arrest or death during the dipyridamole–thallium-201 protocol. Symptomatic or electrocardiographic evidence of ischemia occurred in 46% of patients, a rate somewhat higher than the 36% reported in other series.[15] As in previous reports, hemodynamic changes during dipyridamole infusion were very modest with a mean peak rate-pressure product of under 11,000 beats/min × mm Hg. In the absence of major changes in determinants of myocardial oxygen demand, ischemia developing in response to dipyridamole may be the result of a "coronary steal" phenomenon, as suggested by others.[16,17,22] Importantly, each episode of dipyridamole-induced ischemia either resolved spontaneously or was rapidly reversed with theophylline, a direct antagonist of dipyridamole's effects, and no patient had a complication related to ischemia. Furthermore, theophylline, while nominally possessing sympathomimetic activity, caused a decrease in heart rate and rate-pressure product when

used in this setting and dosage. One patient developed an acute ischemic episode 8 hours after the dipyridamole–thallium-201 study. However, the coronary effects of dipyridamole persist for only 20 minutes[23] and the systemic hemodynamic effects subsided by 15 minutes in our study. In addition, this patient had neither dipyridamole-induced chest pain nor ST depression. Therefore, it is highly unlikely that his ischemic episode 8 hours later can be attributed to an adverse effect of dipyridamole.

Nevertheless, our study cohort was relatively small and we advise caution regarding the safety of dipyridamole–thallium-201 imaging early after infarction until our results are confirmed by other larger studies. Furthermore, because approximately half the patients developed evidence of ischemia during dipyridamole infusion, we strongly advise that dipyridamole–thallium-201 imaging in this setting be performed by experienced physicians familiar with the treatment of dipyridamole-induced ischemia. Finally, our hemodynamic and safety data may not apply to the use of high-dose oral dipyridamole, which many nuclear imaging laboratories now use because the intravenous preparation is not yet commercially available.[24,25] Oral administration of high-dose dipyridamole has distinct disadvantages in the patient after AMI, including wide variability of absorption and time to peak effect,[24,25] and we would not currently advocate its use in this setting.

Timing of thallium-201 imaging after infarction: Experimental studies have shown that myocardial thallium-201 uptake immediately after infarction (<1 hour) is related only to blood flow and cannot distinguish viable from irreversibly injured myocardial cells,[26–28] although some indirect data from clinical studies appear to contradict this.[29] In either case, by 24 to 48 hours thallium-201 is taken up only by viable myocardium.[27,28] Thus, thallium-201 myocardial imaging can be applied very early in care after myocardial infarction. Furthermore, there is accumulating evidence that coronary angioplasty performed acutely in the setting of thrombolytic therapy for myocardial infarction has a relatively high risk of early recurrent occlusion.[7,30] Therefore, investigators have recently advocated waiting at least several days after myocardial infarction before performing angioplasty.[7,30] Our results suggest that dipyridamole–thallium-201 imaging may be able to provide important prognostic information before that time and allow a more directed approach of revascularization interventions after infarction, taking into consideration those most likely to benefit from such procedures.

Study limitations: The study cohort represents a relatively small sample of all eligible patients. This reflected a combination of factors, including a limitation in our ability to accommodate research thallium-201 studies on very short notice in a very busy clinical nuclear cardiology laboratory, as well as a reluctance of some patients to enter a research protocol. Clearly, better access to nuclear cardiology facilities will be required for widespread application. On the other hand, we found that the large majority of patients admitted with an AMI were eligible for our study and could potentially benefit from early risk stratification. Moreover, our study cohort was quite typical of the larger group of patients who were eligible (Table I). Although there were relatively few non-Q-wave myocardial infarctions in the study cohort, the frequency of non-Q-wave infarctions was not significantly different from that of the nonenrolled eligible group (Table I). Nevertheless, conclusions regarding the prognostic value of early postinfarction dipyridamole–thallium-201 in non-Q-wave infarctions must be considered very limited. Finally, our distinction between infarct zone and noninfarct zone redistribution is limited by the specificity of electrocardiographic localization using Q waves. However, no patient in our study had only noninfarct zone thallium-201 redistribution.

Conclusions: Our results suggest that infarct zone thallium-201 redistribution in dipyridamole–thallium-201 studies very early after myocardial infarction identifies a subgroup of patients at high risk for early and late ischemic cardiac events who may benefit from early elective invasive diagnostic or therapeutic procedures. In contrast, patients without infarct zone thallium-201 redistribution appear to be at very low risk for in-hospital and late ischemic cardiac events.

Acknowledgment: We gratefully thank Ruth Mickey, PhD (Biometry Department, University of Vermont College of Medicine), for expert help with statistical analysis; Nancy Perrine and Michaelanne Martello for superb assistance in preparation of the manuscript; Richard Lew, ARRT-N, Linda Benoit, ARRT-N, Edward Tumielewicz, ARRT-N, and Josie LaMountain, RN, for skilled technical assistance; Martin LeWinter, MD, Roy Ditchey, MD, and Bryan Slinker, PhD, for helpful review of the manuscript; and Chris Weinheimer for retrieval of patient expenses and length of stay information.

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Elevation of C-Reactive Protein in "Active" Coronary Artery Disease

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Unstable angina occurs most commonly in the setting of atherosclerotic coronary artery disease (CAD), but there is little information concerning the mechanisms responsible for the transition from clinically stable to unstable coronary atherosclerotic plaque. Recently, increased focal infiltration of inflammatory cells into the adventitia of coronary arteries of patients dying suddenly from CAD and activation of circulating neutrophils in patients with unstable angina have been observed. To characterize the presence of inflammation in "active" atherosclerotic lesions, the acute phase reactant C-reactive protein (CRP) was measured in 37 patients admitted to the coronary care unit with unstable angina, 30 patients admitted to the coronary care unit with nonischemic illnesses and 32 patients with stable CAD. CRP levels were significantly elevated (normal <0.6 mg/dl) in 90% of the unstable angina group compared to 20% of the coronary care unit group and 13% of the stable angina group. The average CRP values were significantly different ($p = 0.001$) for the unstable angina group (2.2 ± 2.9 mg/dl) compared to the coronary care (0.9 ± 0.7 mg/dl) and stable angina (0.7 ± 0.2 mg/dl) groups. There was a trend for unstable angina patients with ischemic ST-T-wave abnormalities to have higher CRP values (2.6 ± 3.4) than those without electrocardiographic changes (1.3 ± 0.9, $p = 0.1$). The data demonstrate increased levels of an acute phase reactant in unstable angina. These findings suggest that an inflammatory component in "active" angina may contribute to the susceptibility of these patients to vasospasm and thrombosis.

(Am J Cardiol 1990;65:168–172)

The syndrome of unstable angina is a dramatic presentation of coronary atherosclerosis that frequently progresses to myocardial infarction. However, it may also revert to a stable anginal pattern even without mechanical relief of the stenosis. While vasospasm[1] and thrombosis[2,3] have been clearly implicated in the pathophysiology of myocardial infarction, the underlying causes for unstable angina are not precisely known. The episodic nature of unstable angina and the frequent lack of correlation between the extent of stenoses and clinical instability raise the possibility that cyclic changes in the activity of the atherosclerotic process itself may be involved. Although the cell biology of atherosclerosis has not been defined completely, the macrophage is now viewed as playing a central role,[4] suggesting that there are some features common to atherosclerosis and inflammatory responses. Although speculative, it is possible that inflammation of coronary arteries may play a role in unstable angina. This proposal is based on the pathologic finding of coronary artery adventitial lymphocytes[5,6] and mast cells[7] at sites of acute thrombosis in patients who have had sudden cardiac death. A causative link between inflammation and thrombosis may be the macrophage-derived inflammatory mediator, interleukin 1, which can induce procoagulant activity in endothelium,[8] thereby converting the endothelium from a nonthrombogenic to a thrombogenic surface. Interleukin 1 may also have an effect on vascular reactivity since it is both a vascular smooth muscle vasodilator[9] and mitogen.[10] These observations link inflammatory responses present in patients with sudden cardiac death to the active atherosclerotic process and thromboses, which appear to be the proximate cause of death. To investigate whether inflammation is present in patients with coronary artery disease (CAD), we measured blood levels of an interleukin 1-induced acute phase reactant, C-reactive protein (CRP),[11] in 3 groups of patients with cardiac disease.

METHODS

Patient population: Three groups of patients were studied. All patients were studied prospectively without knowledge of CRP levels. The protocol was approved by the Institutional Review Boards for Research Involving Human Subjects. The first group consisted of patients consecutively admitted to the coronary care unit during a 6-month period. These patients were divided into 2 groups (described below) based on whether their admitting diagnosis was related to coronary ischemia or other cardiac illness (primarily heart failure and cardiac arrhythmia). Patients who had had a myocardial infarction or had undergone major surgery within the previous 10 days were excluded. Patients who evolved a myo-

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TABLE I Clinical Characteristics of the Three Study Groups

	Unstable Angina	Nonischemic Coronary Care	Stable Angina	p Value*
Pts (n)	39	30	32	NS
Age (yrs)	63 ± 16	57 ± 16	59 ± 9	NS
Sex: M/F	21/18	11/19	26/6	0.002 (NS, 0.015)
Rest angina	30	6	3	0.001 (0.001, 0.001)
Change in pain	37	10	0	0.001 (0.001, 0.001)
Past myocardial infarct	14	6	12	NS
Congestive heart failure	6	7	2	NS
Cigarette smoker	16	9	14	NS
Diabetes mellitus	10	4	3	NS
Blood pressure >150/90 mm Hg	20	9	10	NS
Total serum cholesterol (mg/dl)	246 ± 57	218 ± 80	232 ± 48	NS
Current medications				
β blockers	23	7	20	0.003 (0.003, NS)
Calcium antagonists	22	9	23	0.004 (0.030, NS)
Diuretics	11	13	4	0.025 (NS, 0.110)
Nitrates	24	9	23	0.003 (0.009, NS)
Aspirin	3	0	6	0.033 (NS, 0.160)
C-reactive protein (mg/dl)	2.2 ± 2.9	0.9 ± 0.7	0.7 ± 0.2	0.001 (0.020, 0.004)

* Comparisons between patient study groups were initially performed by chi-square tests for discontinuous variables and by 1-way analysis of variance for continuous variables. Where significant differences ($p < 0.05$) were present, subgroup analysis was performed using an unpaired *t* test with a Bonferroni correction. The subgroup analyses are shown to the right of the p value in parentheses. The values represent the p value for comparison of unstable angina patients with nonischemic coronary care and stable angina patients, respectively.
NS = not significant.

cardial infarction, diagnosed by the demonstration of 2 serial creatine kinase-MB values above normal, were also excluded. Of 100 consecutive patients admitted, a total of 69 patients met the inclusion criteria. The third group consisted of 32 patients with stable CAD. They were consecutive patients electively referred during 1 week to the hospital for cardiac catheterization, for coronary artery bypass surgery of stable disease or for participation in an ambulatory Holter monitoring study.

Diagnosis of unstable angina: Unstable angina was diagnosed based on the criteria used by Lewis et al[12] in the Veterans Administration Cooperative Study. All of the following were required: unstable angina beginning within the previous month and still present within 48 hours of admission, evidence of CAD and absence of baseline evidence of acute myocardial infarction as determined by electrocardiography (new Q-wave or persistent ST-segment elevation) or elevation of creatine kinase-MB enzymes (2 serial values above normal). Unstable angina was defined as new onset or sudden worsening of angina without increased activity occurring ≥1 time/day, a single episode lasting ≥15 minutes or occurrence at rest or during minimal activity. Evidence of CAD was defined by 1 or more of the following: electrocardiogram or hospital record evidence for prior myocardial infarction, electrocardiographic changes consisting of transient ST-segment elevation or depression of 0.1 mV lasting for 0.08 second, previous coronary arteriograms showing at least 75% narrowing, previous exercise tolerance test meeting the criteria for ST-segment depression already given or a history of typical exertional chest pain relieved by rest or nitroglycerin.

Coronary angiography: Coronary angiography was performed using the Judkins technique. The percent stenosis of each coronary artery visualized in multiple views was assessed by a consensus reading of 3 observers. For patients in the unstable angina group, a vessel was considered to be significantly narrowed if ≥70% transluminal narrowing was present.

C-reactive protein determination: Following venipuncture, blood samples were centrifuged within 12 hours and stored at 4°C for 1 to 2 days or frozen before assay. CRP was assayed by immunochemical rate nephelometry (Beckman CRP and Beckman Immunochemistry System). Standardization of the CRP assay was performed before each set of assays and had a variation of 10 ± 7% (n = 4). Normal values for CRP using these reagents are <0.6 mg/dl.[13] CRP values for all patients admitted to the coronary care unit were determined on blood samples obtained on admission to the unit (usually within 4 hours of presentation to the hospital). Because there is no evidence for a diurnal variation in CRP levels of the magnitude observed in the unstable angina patients,[11,14–16] blood samples obtained in the morning, on elective presentation to the hospital, were used for the other groups.

Statistical analyses: Data are presented as the mean ± standard deviation or counts. Continuous variables were compared by a 1-way analysis of variance, and where indicated by a subgroup analysis using an unpaired *t* test with a Bonferroni correction. Chi-square tests were used to compare discontinuous variables.

RESULTS

Patient characteristics: The patient profiles of the 3 study groups are listed in Table I. The groups of stable CAD patients and unstable angina patients were very similar in their demographic characteristics. Because the other coronary care unit patients were admitted primarily for cardiac arrhythmias and congestive heart failure, they were younger, more likely to be female, had fewer myocardial infarctions, and were receiving fewer antianginal medications than the other groups. There were 7 patients classified initially with unstable

angina based only on clinical symptoms consisting of a change in their typical exertional chest pain relieved by rest. All of these patients underwent exercise tolerance testing and coronary angiography before discharge. Significant coronary artery stenoses (>70%) were found in 2 patients, while 5 had no narrowings >20%. These 5 patients also had normal exercise tests and therefore were reclassified to the coronary care unit group without unstable angina. Only 1 of these patients had an elevated CRP value.

C-reactive protein measurements: As shown in Figure 1, 35 patients (90%) with a final diagnosis of unstable angina had CRP values (range 0.65 to 15.0 mg/dl) above the upper limit of normal (<0.6 mg/dl). In contrast, only 6 patients (20%) in the coronary care unit group and 4 patients (13%) in the stable CAD group had elevated CRP levels (range 0.66 to 3.0 mg/dl). The mean CRP values for the 3 groups, after assigning a value of 0.6 mg/dl to patients with CRP values undetectable by rate nephelometry (this is a maximal value), were 2.2 ± 2.9, 0.9 ± 0.7 and 0.7 ± 0.2, respectively. The difference between the unstable angina group and the other 2 groups is significant ($p = 0.001$). This difference is even larger when those patients in the other 2 groups with elevated CRP values likely due to coexisting inflammatory diseases are excluded. The most common diagnosis made in association with elevated CRP in the absence of unstable angina (6 patients) was arthritis (osteoarthritis, rheumatoid, costochondritis or gout). No patients with elevated CRP levels had clinical findings suggestive of an acute infectious process. CRP values among patients with stable CAD did not differ from values found in patients in the coronary care unit who did not have unstable angina. This indicates that elevation of CRP in patients with unstable angina was not a consequence of procedures associated with the coronary care unit.

In our study, 11 patients admitted to the coronary care unit with a diagnosis of unstable angina were found to have increased creatine kinase-MB values within 4 hours of admission. They were excluded from subsequent analysis because of presumed myocardial infarction. The CRP values for all these patients were elevated, with an average for the group of 5.2 ± 3.3, which is consistent with values reported previously.[14-16]

Electrocardiographic changes and C-reactive protein values: Approximately 70% of the study patients with unstable angina had electrocardiographic changes at rest in the coronary care unit. Analysis of the CRP values in unstable angina patients with ST-T-wave abnormalities suggested that these patients had higher values (2.6 ± 3.4) than patients with unstable angina but no electrocardiographic changes (1.3 ± 0.9, $p = 0.1$).

Temporal changes in C-reactive protein values: Unstable angina is a dynamic disease with rapid fluctuations in symptoms. In several reports of CRP measurements in myocardial infarction, sudden increases in CRP levels were observed in association with recurrent symptoms, suggesting that CRP is a dynamic marker of inflammation. To gain insights into the temporal relation between CRP values and unstable angina we studied 2 patients with unstable angina associated with particularly prominent and frequent electrocardiographic changes (ST-segment depressions of >0.3 mm, occurring >3 times/day). As shown in Figure 2 there were significant fluctuations in CRP values that bore some association with both clinical symptoms and electrocardiographic changes. In patient 2 the inability to manage unstable angina medically was mirrored in the progressive increase in CRP before coronary artery bypass surgery.

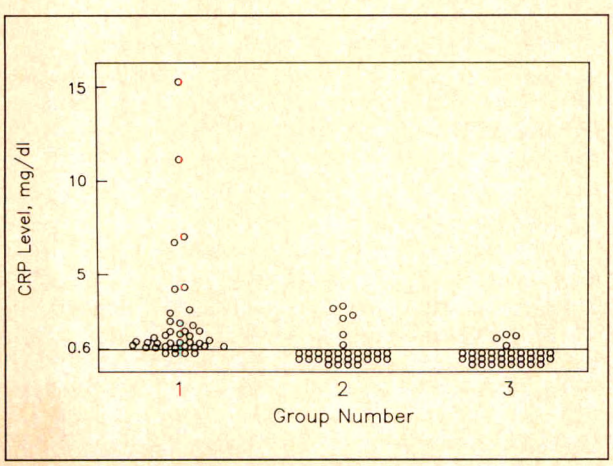


FIGURE 1. C-reactive protein (CRP) levels in 101 patients characterized by diagnostic groups. CRP values below normal (<0.6 mg/dl) were not further quantitated and are shown as 0.6 mg/dl. Group numbers *1, 2* and *3* correspond to patients with unstable angina, patients in the coronary care unit with nonischemic diseases and patients with stable CAD, respectively. The means (± standard deviations) for the groups were significantly different ($p = 0.001$) with subgroup analysis yielding significant differences between groups 1 and 2 ($p = 0.02$) and 1 and 3 ($p = 0.004$), but not between groups 2 and 3.

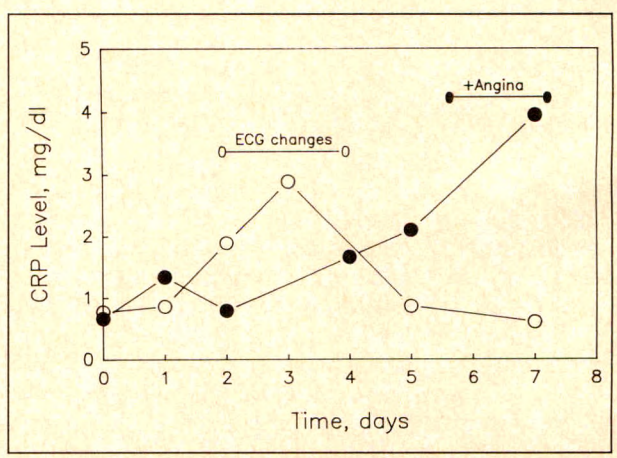


FIGURE 2. Serial C-reactive protein (CRP) levels after admission in 2 patients with unstable angina. CRP levels were determined from daily venous blood samples drawn in the morning. Initial CRP values were 0.8 and 0.7 mg/dl in patients 1 and 2, respectively. Patient 1 (*open circles*) developed 2 mm of ST-segment depression during day 2, which resolved after administration of heparin on day 3. Patient 2 (*filled-in circles*) developed increasing angina at rest despite maximal medical therapy and underwent coronary artery bypass surgery for severe 3-vessel disease on day 8.

DISCUSSION

The observation that CRP values are elevated in patients with unstable angina clearly indicates that a consequence of the "active" coronary atherosclerotic lesion is inflammation or tissue injury, or both. A central issue is whether this inflammatory response results from events occurring solely at the active lesion itself or is also, in part, a consequence of myocardial injury/ischemia downstream from the epicardial coronary artery lesion.

Inflammation in the atherosclerotic lesion: Wallsh et al[17] noted during surgery that 21 patients undergoing coronary artery bypass surgery for unstable angina had "red lines" overlying 1 or more coronary arteries. Adventitial biopsies revealed inflammatory cell nests and neovascularization. There is considerable pathologic evidence of inflammation in coronary arteries of patients dying suddenly of myocardial infarction. Increased adventitial round cell[5,6] and mast cell[7] infiltrates have been observed in the coronary vessels of such patients. Because the most intense infiltration is frequently present in the area of an occlusive thrombus, it has been proposed that the inflammatory response preceded the terminal event and may have been causally related both to the infarction and to the preceding unstable angina.[5]

There is angiographic evidence that unstable angina occurs in the setting of rapidly progressive CAD.[18] This suggests that the cellular basis of clinical instability reflects mitogenic influences and cellular proliferation in the intimal lesion.[19] Data from studies on the pathogenesis of atherosclerosis in animal models indicate that macrophage-derived factors may be important in smooth muscle cell chemotaxis and proliferation.[20] The central role of the macrophage in inflammation implies that this process and atherosclerosis have certain common features. Thus the presence of elevated CRP in "active" angina syndromes may reflect increased macrophage activity in the coronary atherosclerotic lesion causing this disease.

In addition to macrophages, T cells have been demonstrated in both early and advanced intimal lesions. Jonasson et al[21] observed that about 20% of the cell population in fibrous carotid atheromas expressed the T3 (CD3) antigen. Furthermore, smooth muscle cells in atherosclerotic plaque (but not normal vessels) express class II MHC (Ia) antigens[22] as do cells from balloon deendothelized arteries.[23] This suggests that lymphokines released by T cells may be responsible for alterations in smooth muscle cell function in atherosclerosis.

Inflammation in the myocardium: An alternative, but not necessarily exclusive, explanation for increased CRP levels in "active" CAD is myocardial inflammation. It is possible that myocardium repeatedly made ischemic may itself incite an inflammatory response. Subtle myocardial injury as a consequence of microembolization from the surface of an ulcerated plaque may also occur.[2] In our study population such putative microinfarctions would have to be so small as not to elevate creatine kinase-MB above normal since we excluded patients with elevated creatine kinase-MB.

Prior studies of inflammation in coronary disease: Several studies have suggested that increased white blood cell counts correlate with the risk of myocardial infarction.[24,25] Neutrophils in patients with unstable angina or acute myocardial infarction have recently been shown to be activated, as manifest by increased plasma levels of fibrin degradation peptide Bβ, an index of neutrophil elastase release.[26] These data provide further support for a contribution by inflammatory cells to the pathogenetic features of CAD.

There have been several previous studies of CRP in acute coronary syndromes, but their primary focus has been on myocardial infarction.[14–16] DeBeer et al[14] observed no elevation of CRP in patients with stable angina undergoing exercise testing. However, CRP levels were increased in 3 of 7 patients hospitalized with severe chest pain but no infarction. In 10 patients with a presumptive diagnosis of unstable angina, Kushner et al[16] found increased CRP levels in 5 patients. The data in these reports, although not collected with the objective of studying unstable angina, lend credence to our observations.

Physiological and clinical implications: As previously noted, both vasospasm[1] and thrombosis,[2,3] usually considered as independent mechanisms, have been thought to be involved in the pathophysiology of unstable angina. If elevation of CRP in unstable angina is indeed related to a "coronary arteritis," then inflammation may contribute to both vasospasm and thrombosis. The macrophage, in particular, may play a central role because it produces substances (leukotrienes, growth factors and procoagulant activity) that alter both vascular reactivity and thrombogenicity.[27–29] Whatever the mechanisms, the elevation of CRP in unstable angina is consistent with a central role for inflammation in the pathophysiology of "active" CAD.

The clinical utility of measurements of CRP in the diagnosis and management of unstable angina remains to be defined. Although in this limited experience the sensitivity of the test was high, the specificity was unavoidably compromised by the presence of other inflammatory illnesses common in the elderly population with CAD. The data suggest that cardiac-specific markers of inflammation might have diagnostic utility in unstable angina, and that treatment of inflammation might be beneficial. In this context the beneficial effects of aspirin in unstable angina patients in the Veterans Administration Cooperative Study[12] may have reflected decreased inflammation in addition to decreased platelet aggregation.

Acknowledgment: We are indebted to Colin Begg, PhD, Andrew Selwyn, MD, and Michael Rocco, MD, for helpful criticism, and to Joan Barry, BA, for technical assistance.

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Effects of Glutamate on Exercise Tolerance and Circulating Substrate Levels in Stable Angina Pectoris

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The effects of glutamate on exercise tolerance, ischemic threshold and venous substrate concentrations were studied in 20 patients with stable angina pectoris and positive stress tests. Each patient underwent 4 upright bicycle exercise tests on consecutive days. The first and fourth tests were performed without medication while the second and third tests were preceded by a low and high bolus dose of monosodium glutamate, either 0.8 and 1.5 mg/kg body weight intravenously (10 patients) or 40 and 80 mg/kg orally (10 patients). Comparison of the first and fourth tests revealed good reproducibility of electrocardiographic, hemodynamic and metabolic data. Glutamate increased exercise duration ($p < 0.05$) in a dose-related way when given intravenously (59 ± 14 and 153 ± 14 seconds) and when given orally (53 ± 21 and 90 ± 23 seconds; all data are mean ± standard error of the mean). It also delayed the onset of ST-segment depression ($p < 0.05$) by 73 ± 19, 120 ± 23, 62 ± 27 and 80 ± 30 seconds, respectively. Hemodynamics were not changed by glutamate at rest or at comparable workloads, but at onset of ST-segment depression the heart rate-blood pressure product was increased ($p < 0.05$). Glutamate administration induced dose-related 1.5- to 10-fold elevations in plasma glutamate, 15 to 50% decreases in plasma free fatty acids ($p < 0.05$) and 5 to 30% increases in plasma alanine contents. Circulating levels of glucose, lactate, citrate and albumin were not modified by glutamate. No adverse effects were observed. Augmented provision of glutamate improves working capacity and ischemic threshold in patients with stable angina, presumably through a metabolic mechanism.

(Am J Cardiol 1990;65:173–178)

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A number of experimental models have demonstrated that exogenous application of glutamate improves the mechanical function and recovery of ischemic myocardium.[1–4] The exact mechanism of the observed protection is uncertain but has been associated with increased anaerobic energy production.[3–5] It is unknown whether increased provision of glutamate protects against ischemic myocardial damage in man. However, glutamate is the only amino acid taken up by the human heart in measurable amounts and the arteriovenous differences are increased in patients with coronary artery disease.[6] Scintigraphy with thallium-201 and nitrogen-13 glutamate has shown that extraction of glutamate is augmented in acutely ischemic myocardium.[7] Global myocardial extraction of glutamate can be as much as 90% of the arterial contents in patients with coronary artery disease.[8] This suggests almost complete extraction and perhaps insufficient supply of glutamate to ischemic areas. Furthermore, infusion of glutamate and glutamate-enriched cardioplegia have been shown to enhance cardiac performance in patients with cardiac failure.[9,10] We examined whether intravenous and oral glutamate administration could improve the ischemic threshold in patients with stable angina pectoris. We also examined the effects of glutamate on hemodynamics and circulating substrate levels during rest and exercise.

METHODS

Patients: The study included 15 men and 5 women (age 57 ± 2 years). Each fulfilled the inclusion criteria: a history of typical stable effort angina for ≥6 months and development of ≥1 mm ST-segment depression during a prestudy exercise test. Eight patients had a documented history of myocardial infarction >4 months before the study. A coronary angiogram was available in 15 patients and showed ≥50% fixed diameter reduction of at least 1 coronary artery. None of the patients had anginal attacks at rest, congestive heart failure, valvular heart disease, bundle branch or atrioventricular block, severe hypertension or metabolic or electrolyte abnormalities. None received digitalis.

Study protocol: After informed consent was obtained, long-acting antianginal medication was stopped a week before the study. Sublingual nitroglycerin was allowed up to 4 hours before each of the 4 upright bicycle exercise tests performed by every patient in the morning after an overnight fast on 4 subsequent days. No medication was given before the first and fourth

TABLE I Exercise Tolerance

	Intravenous Glutamate (n = 10)				Oral Glutamate (n = 10)			
Exercise Test No.	1	2	3	4	1	2	3	4
Dose of Glutamate (mg/kg body weight)	0	0.8	1.5	0	0	40	80	0
Exercise duration (s)	319 ± 36	378 ± 38†	472 ± 51†	359 ± 39	373 ± 41	426 ± 49*	463 ± 49†	402 ± 42*
Time to onset of ST-depression (s)	165 ± 28	238 ± 41*	285 ± 38‡	166 ± 28	244 ± 30	306 ± 46*	324 ± 45*	267 ± 44
Maximum ST-depression (mm)	2.1 ± 0.2	2.2 ± 0.2	1.8 ± 0.2	2.0 ± 0.2	2.1 ± 0.3	1.8 ± 0.3	1.9 ± 0.4	2.0 ± 0.2
Angina (none/slight/moderate/severe)	0/2/6/2	2/1/6/1	2/2/5/1	1/2/6/1	0/5/3/2	2/3/3/2	3/3/3/1	2/2/4/2

Date are mean ± standard error of the mean.
Difference from respective values in test no. 1: * $p < 0.05$, † $p < 0.01$, ‡ $p < 0.001$.

TABLE II Hemodynamics

	Intravenous Glutamate (n = 10)				Oral Glutamate (n = 10)			
Test No.	1	2	3	4	1	2	3	4
Dose of Glutamate (mg/kg body weight)	0	0.8	1.5	0	0	40	80	0
Heart rate (beats/min)								
At rest	81 ± 5	83 ± 6	86 ± 6	81 ± 5	74 ± 4	78 ± 4	79 ± 4	77 ± 3
Exercise after (2)-5 minutes	126 ± 6	125 ± 7	123 ± 5	124 ± 6	118 ± 6	120 ± 6	127 ± 5	122 ± 5
Exercise at onset of ST depression	112 ± 6	125 ± 7*	126 ± 4†	114 ± 5	111 ± 6	117 ± 5*	121 ± 6†	113 ± 4
Exercise at end	133 ± 7	138 ± 6	139 ± 5	133 ± 6	126 ± 6	129 ± 6	134 ± 6	130 ± 5
Recovery at 30 minutes	79 ± 5	80 ± 4	83 ± 5	82 ± 3	76 ± 4	72 ± 2	79 ± 3	75 ± 3
Systolic arterial pressure (mm Hg)								
At rest	137 ± 4	136 ± 5	121 ± 4†	123 ± 5†	123 ± 4	119 ± 3	115 ± 4	116 ± 4
Exercise after (2)-5 minutes	154 ± 6	155 ± 4	152 ± 5	145 ± 5	141 ± 7	146 ± 7	146 ± 8	141 ± 7
Exercise at onset of ST depression	149 ± 5	159 ± 6†	154 ± 6	147 ± 4	144 ± 6	151 ± 7	151 ± 7	140 ± 8
Exercise at end	158 ± 7	167 ± 7*	163 ± 7	158 ± 7	150 ± 7	161 ± 7*	162 ± 8*	151 ± 7
Recovery at 30 minutes	129 ± 6	121 ± 4	121 ± 4*	120 ± 5*	120 ± 4	115 ± 3	117 ± 4	114 ± 3
Mean arterial pressure (mm Hg)								
At rest	106 ± 2	105 ± 3	97 ± 3†	98 ± 3*	94 ± 3	90 ± 3	89 ± 2	91 ± 3
Exercise after (2)-5 minutes	113 ± 3	112 ± 3	112 ± 3	106 ± 2	103 ± 4	103 ± 5	101 ± 6	100 ± 4
Exercise at onset of ST depression	111 ± 3	115 ± 3*	112 ± 2	106 ± 2	103 ± 4	107 ± 4	106 ± 4	100 ± 4
Exercise at end	115 ± 4	119 ± 4	118 ± 3	113 ± 4	107 ± 4	111 ± 4	111 ± 6	106 ± 4
Recovery at 30 minutes	101 ± 3	97 ± 2†	95 ± 3	95 ± 3	93 ± 3	90 ± 2	91 ± 3	88 ± 2†
Rate-pressure product (mm Hg × beats/min × 0.01)								
At rest	111 ± 9	114 ± 11	104 ± 7	99 ± 8*	91 ± 5	93 ± 6	92 ± 6	89 ± 4
Exercise after (2)-5 minutes	195 ± 13	194 ± 11	188 ± 11	180 ± 11	168 ± 14	177 ± 16	179 ± 15	173 ± 13
Exercise at onset of ST depression	167 ± 1	199 ± 14*	197 ± 12*	172 ± 8	158 ± 15	175 ± 15*	181 ± 15†	157 ± 14
Exercise at end	213 ± 16	220 ± 16	228 ± 15	210 ± 16	188 ± 16	206 ± 15	212 ± 16*	192 ± 15
Recovery at 30 minutes	104 ± 9	98 ± 7	101 ± 7	99 ± 7	91 ± 6	84 ± 4	90 ± 4	87 ± 4

Data are mean ± standard error of the mean.
Difference from respective values in test no. 1: * $p < 0.05$, † $p < 0.01$.

tests. The second and third tests were preceded by a bolus dose of monosodium glutamate—either 0.8 and 1.5 mg/kg body weight given intravenously 5 minutes before exercise (10 patients) or 40 and 80 mg/kg given orally 30 minutes before start of exercise (10 patients). A solution of 25 mg/ml (170 μmol/liter) monosodium glutamate was used for intravenous injection while each oral dose of crystalline monosodium glutamate was dissolved in 50 ml of water just before ingestion. The patients were questioned daily about subjective adverse drug effects.

During each exercise test the initial workload of 50 watts was increased by 50 watts every 3 minutes until angina, dyspnea or exhaustion occurred and the test was stopped. Blood pressure was measured by arm cuff. Six-lead electrocardiograms (standard leads I, II, III and precordial leads V_2, V_5, V_6) were recorded continuously, and heart rate, ST-segment displacement 0.08 second after the J point and blood pressure were measured every minute from 1 minute before to 5 minutes after end of exercise and at 15 and 30 minutes of recovery. Intensity of anginal pain at the end of exercise was assessed as slight, moderate or severe (below, similar to or above the level of pain at which the patient normally would take sublingual nitroglycerin).

Blood samples were drawn from an antecubital vein at identical times during the 4 tests in each patient: before glutamate administration and 1 minute before start of exercise; at 5 minutes after start and at stop of exercise; and at 15 and 30 minutes of recovery. In case the first exercise test was stopped before 5 minutes, blood samples were drawn after a similar exercise duration in the following tests. The blood samples were prepared and analyzed for contents in whole blood of lactate and in plasma of albumin, free fatty acids, glucose, citrate, glutamate and alanine as described earlier.[6]

Calculations and statistics: The rate-pressure product was determined as the systolic blood pressure multiplied by heart rate. Values are mean ± standard error of the mean. The paired *t* test, Wilcoxon signed rank test and linear regression analysis were used for statistics. Statistical significance was assumed at $p < 0.05$.

RESULTS

Mean doses of monosodium glutamate given before the second and third tests were 62 ± 2 and 115 ± 4 mg intravenously and 2.8 ± 0.1 and 5.7 ± 0.2 g orally. Two patients complained of headache after the highest oral dose but none reported adverse effects after intravenous glutamate administration.

Exercise duration, ST depression and angina: Exercise duration was increased after glutamate, when compared to the first test (Table I). The exercise prolongations were dose-related both when glutamate was given intravenously (low vs high dose: 59 ± 14 vs 153 ± 14 seconds, $p < 0.05$) and orally (53 ± 21 vs 90 ± 23 seconds, difference not significant). Despite no medication, exercise duration in the fourth test also tended to be higher than during the first test (40 ± 20 seconds [difference not significant] in the intravenously and 29 ± 10 seconds [$p < 0.05$] in the orally treated group). Exercise prolongations after high but not after low dose glutamate were, however, higher than these spontaneous prolongations in both groups ($p < 0.05$).

The onset of ≥1 mm of ST-segment depression during exercise was delayed after glutamate ($p < 0.05$) in a dose-related manner, both when given intravenously (low vs high dose: 73 ± 19 vs 120 ± 23 seconds, $p < 0.02$) and orally (62 ± 27 vs 80 ± 30 seconds, difference not significant). Maximal ST depression was not influenced by the drug. Neither time to nor magnitude of ST-segment depression differed between the first and fourth test in the 2 groups.

All patients stopped the first exercise test because of angina. Glutamate tended to relieve or even abolish exercise-induced chest pain but without reaching statistical significance. The degree of pain varied, although not significantly, between the first and fourth test.

Hemodynamics: The first and fourth tests showed good reproducibility of heart rate, blood pressure and rate-pressure product (Table II). The rate-pressure product at onset of ST-segment depression was increased by both intravenous ($p < 0.05$) and oral ($p < 0.05$) glutamate, but glutamate did not consistently change hemodynamic values when they were measured at rest, after comparable durations of exercise or during recovery.

Circulating substrates: Comparison of group mean data in the first and fourth tests revealed a good reproducibility of the basal venous substrate concentrations and of the metabolic response to exercise (Figure 1).

Plasma glutamate levels were not influenced by exercise in the control tests. Intravenous glutamate administration rapidly increased the plasma content from 38 ± 4 to 67 ± 5 μmol/liter ($p < 0.01$) after the low dose and from 38 ± 3 to 91 ± 14 μmol/liter ($p < 0.001$) after the high dose. Mean peak plasma levels observed after ingestion of glutamate were 99 ± 12 μmol/liter after the low dose and 260 ± 31 μmol/liter after the high dose. Despite rapid clearance of plasma glutamate, the concentrations remained above control values until the end of exercise both after intravenous and oral administration.

Mean plasma albumin concentrations in all tests increased from 617 ± 9 at rest to 651 ± 7 μmol/liter at peak exercise ($p < 0.001$) and returned to 619 ± 5 μmol/liter after 15 minutes of recovery. Glutamate pretreatment did not modify this exercise-induced hemoconcentration.

Basal plasma glucose levels ranged from 4.37 to 5.98 with an overall mean value of 5.26 ± 0.05 mmol/liter. Neither exercise nor glutamate induced any significant changes in plasma glucose concentrations.

Blood lactate accumulated significantly within 2 to 5 minutes of exercise in every test with an overall mean value of 2.08 ± 0.10 versus a resting level of 1.24 ± 0.05 mmol/liter ($p < 0.001$). Glutamate did not change lactate levels at rest or during early exercise. Peak lactate concentrations at end of exercise tended to be increased in a dose-related manner after glutamate when compared to the first test, but this did not reach significance whether given intravenously (4.06 ± 0.70 and 4.11 ± 0.44 vs 3.10 ± 0.36 mmol/liter) or orally (3.90 ± 0.58 and 4.37 ± 0.36 vs 3.63 ± 0.67 mmol/liter). Maximal percentage increase in blood lactate was positively related to exercise duration in all tests ($r = 0.44$, $p < 0.001$) regardless if they were performed with ($r = 0.40$, $p < 0.01$) or without ($r = 0.55$, $p < 0.001$) glutamate pretreatment.

Plasma alanine increased during each control test, reaching significance at 2 to 5 minutes of exercise ($p < 0.05$) and maximum at 15 minutes of recovery ($p < 0.01$). Overall mean values in the first and fourth tests were 323 ± 8 at rest, 347 ± 11 at early exercise and 376 ± 12 μmol/liter at 15 minutes of recovery. This exercise-induced elevation of plasma alanine was augmented by glutamate treatment in a dose-related way. Peak alanine levels at 15 minutes of recovery were higher than control values after oral low dose (435 ± 25 μmol/liter, $p < 0.05$), oral high dose (476 ± 27 μmol/liter, $p < 0.001$) and intravenous high dose (411 ± 29 μmol/liter, $p < 0.05$), but not after intravenous low dose (400 ± 29 μmol/liter, difference not significant).

Plasma free fatty acid concentrations decreased during exercise in the first and fourth tests from an average of 742 ± 67 to 442 ± 51 μmol/liter ($p < 0.001$) in the intravenously treated group and from 485 ± 42 to 346 ± 25 μmol/liter in the orally treated group. The free fatty acid levels returned to resting values at 15 minutes of recovery in the control tests. After glutamate administration plasma free fatty acids were decreased even in the resting state (to 621 ± 90 [$p < 0.05$] and 550 ± 68 μmol/liter [$p < 0.005$] after low and high doses intravenously and to 348 ± 31 [$p < 0.02$] and 341 ± 46 μmol/liter [$p < 0.01$] after low and high doses orally). This decrease continued during exercise, reaching nadir values of 421 ± 101 ($p < 0.001$), 368 ± 72 ($p < 0.001$), 205 ± 30 ($p < 0.001$) and 194 ± 21 ($p < 0.001$) μmol/liter, respectively. The fatty acid concentration remained significantly below pretreatment and control levels throughout the recovery period after glutamate ingestion, but returned to normal values during recovery in the intravenously treated group.

In every control test plasma citrate concentrations increased significantly ($p < 0.01$) above resting level (overall mean 120 ± 4 μmol/liter) after end of exercise. They reached peak values at 30 minutes of recovery

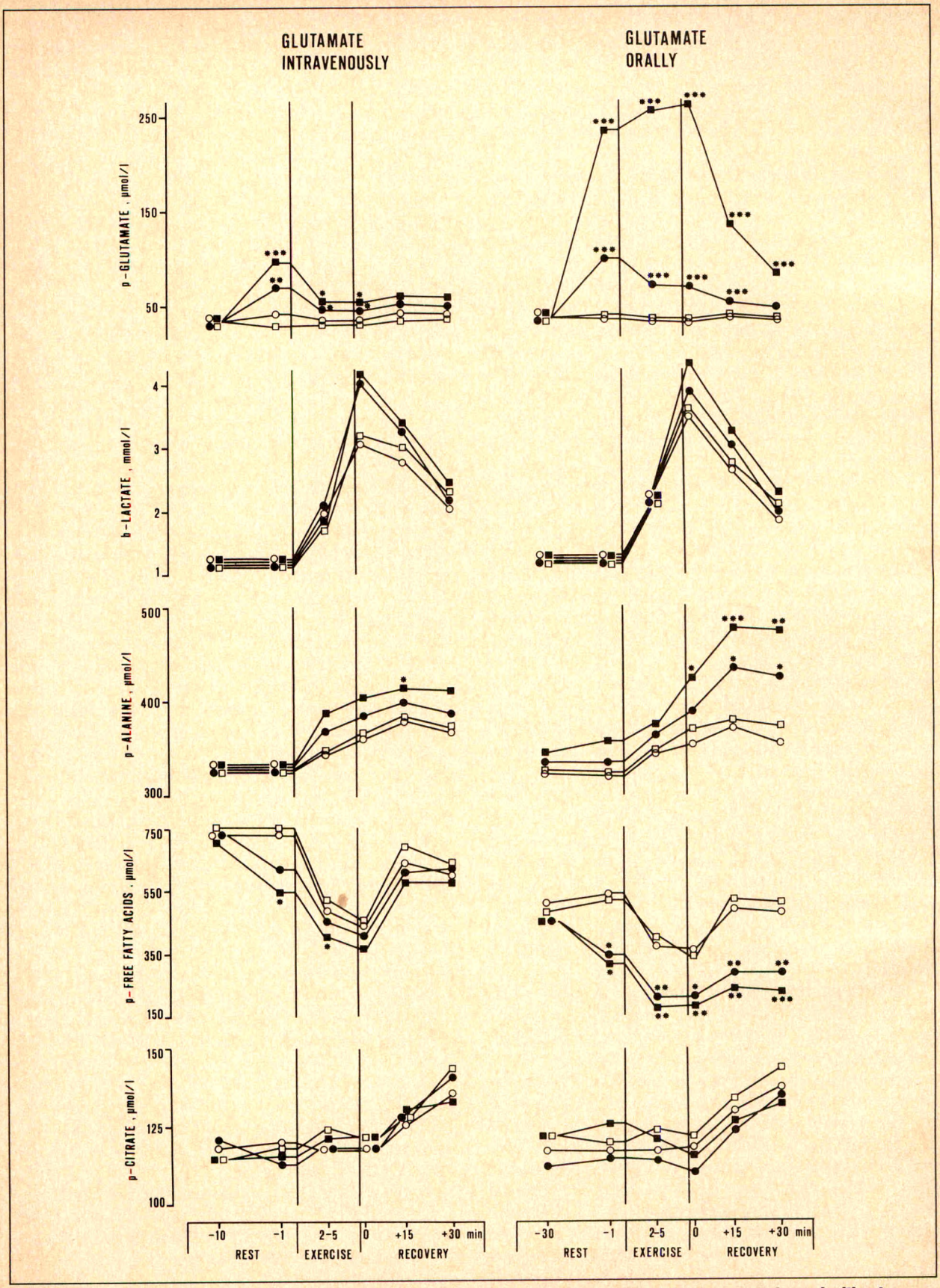


FIGURE 1. Mean venous substrate concentrations during 4 exercise tests. Tests 1 (○) and 4 (□) were performed without medication while a low (•) and high (■) dose of monosodium glutamate was given intravenously (10 patients) or orally (10 patients) after the first sample in tests 2 and 3. In every patient, blood samples were drawn at the same time after start of exercise in each of the 4 tests. Exercise duration at sampling varied from 2 to 5 minutes between patients. Difference from respective values versus test no. 1: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

(140 ± 4 μmol/liter). Glutamate administration did not affect plasma citrate concentrations at rest or during or after exercise.

DISCUSSION

Working capacity and ischemic threshold were enhanced in patients with stable angina pectoris after intravenous and oral administration of glutamate. The improvement was accompanied by 1.5- to 7-fold elevations of circulating glutamate levels, pronounced decreases in plasma free fatty acids and accentuation of exercise-induced increases of plasma alanine. Glutamate was well tolerated and rapidly metabolized.

This was a pilot study and neither the optimal dose, route of administration nor chemical form of glutamate for the treatment of ischemic heart disease in man was established. The beneficial cardiac effects of propranolol are associated with a 20% increase of arterial glutamate levels[11] whereas much higher concentrations (6- to 16-fold times physiologic levels) have been used in most studies of the cardioprotective effects of glutamate.[1–5,10] We used the monosodium salt of glutamic acid and intended to achieve peak elevations of plasma glutamate ranging from 20 to 800%. Actual doses were chosen on the basis of previous pharmacokinetic reports.[12] Side effects, including burning sensations, facial pressure and chest pains, are seldom noted after these doses[13] and were not observed in this study.

Oral glutamate has to be dissolved in water to ensure rapid significant increases in plasma levels.[12] The characteristic taste of monosodium glutamate has no placebo equivalent[14] and makes it virtually impossible to design a blind study. The open design of the present study is, however, a major point of concern because placebo effects must be expected.[15] Anginal pain and working capacity are especially subject to the influence of placebo effects while hemodynamic and electrocardiographic changes are less influenced.[15] Accordingly, in this as in other studies,[16,17] anginal pain and duration of work tended to vary when exercise testing without medication was repeated, whereas rate-pressure product and ST-segment depressions were reproducible. Therefore the delayed onset of ST-segment depression at an increased rate-pressure product after glutamate treatment suggests more specific physiologic actions on myocardial ischemic disease. The beneficial effects were dose-related whether glutamate was given orally or intravenously.

General hemodynamics both at rest and at comparable workloads were unchanged by glutamate administration, suggesting its effects to be mainly metabolic. Anaerobic adenosine triphosphate production may be increased by conversion of glutamate to succinate,[3,5] but carbohydrate remains the most important energy source during ischemia.[18] The initial high rates of glycolysis are, however, rapidly inhibited due to accumulation of lactate and reduced nicotinamide-adenine dinucleotide.[19,20] Glutamate may diminish lactate accumulation by transamination with pyruvate leading to the production of alanine instead of lactate.[5,21] Removal and reoxidation of cytosolic reduced nicotinamide-adenine dinucleotide occurs via the malate-aspartate cycle.[22,23] Flux through this shuttle is partly regulated by cytosolic glutamate concentration[22] and requires import of glutamate.[23] Via these involvements, glutamate may be of importance for the maintenance of increased glycolysis during ischemia.[8] In fact, increased glucose breakdown has been reported in isolated myocytes when glutamate is present as the second substrate.[24]

This study does not provide insight into the exact mechanism by which glutamate exerted its beneficial effects. Glutamate administration increased plasma alanine but did not affect blood lactate concentrations. This supports the supposition that glutamate transaminates with pyruvate[5,21] and that it may stimulate glycolysis without increasing lactate production. The pronounced depression of circulating free fatty acids seen after glutamate administration may additionally enhance carbohydrate utilization due to a diminished substrate competition.[19] The decrease of free fatty acids had occurred in the resting state before the onset of exercise, which is known to be associated with an early transient reduction of plasma free fatty acids.[25] The mechanism behind the antilipolytic effect of glutamate is so far unknown.

These results suggest a cardioprotective action of glutamate in man and encourage more extensive studies of its cardiac metabolic effects.

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Influence of Heparin Therapy on Percutaneous Transluminal Coronary Angioplasty Outcome in Patients with Coronary Arterial Thrombus

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The clinical and angiographic outcome of 18 patients with coronary thrombus undergoing percutaneous transluminal coronary angioplasty without antecedent heparin therapy was compared to that of a group of 35 patients receiving preprocedural heparin therapy. The former group had a significant reduction in angiographic success (61 vs 94%, p <0.05) and a significant increase in immediate postprocedural thrombotic arterial occlusion (33 vs 6%, p <0.05). This difference existed despite equivalent frequencies of antiplatelet therapy. Prolonged intravenous heparin therapy before angioplasty in the setting of coronary thrombus improves the overall success rate and lessens the likelihood of periprocedural coronary arterial thrombosis.

(Am J Cardiol 1990;65:179–182)

Coronary thrombus has been identified as a preprocedural risk factor for an unsuccessful outcome of percutaneous transluminal coronary angioplasty (PTCA).[1–3] The balance between those factors responsible for thrombus formation and propagation and those elements favoring clot lysis may be favorably altered in some circumstances. Specifically, the inhibition of thrombin generation by heparin may not only affect clot propagation and platelet aggregation but also may allow endogenous fibrinolytic mechanisms to operate more efficiently by decreasing the total clot burden. Preliminary reports from uncontrolled studies have suggested that heparin administration before PTCA in the setting of coronary thrombus may decrease the risk of periprocedural thromboembolic complications.[4,5] No study has compared the relative risk of PTCA in the setting of preexistent thrombus in patients with and without prior heparin therapy. Therefore, we retrospectively examined the acute outcome of a consecutive group of patients undergoing PTCA in the setting of intracoronary thrombus with particular attention to the presence or absence of pretreatment with systemic anticoagulation.

METHODS

Nine-hundred two PTCA angiograms performed from January 1985 through December 1987 were reviewed for the presence or absence of preexistent intracoronary thrombus. Patients who were within 24 hours of acute myocardial infarction, who had had thrombolytic therapy within 7 days of PTCA and those with a totally occluded culprit vessel were excluded from analysis. Thrombus was considered present if there was a nonlinear filling defect distinct from the vessel wall on at least 3 borders.[6,7] All PTCA procedures were performed using standard transfemoral Judkins technique and ionic contrast media. Over the time interval of this study, all procedures were performed with the same movable guidewire dilating system (USCI LPS-I). The adequacy of systemic anticoagulation at the outset and during the PTCA was assessed by periodic measurement of the activated clotting time, which in our laboratory is considered satisfactory if >300 seconds. Supplemental bolus intravenous heparin was given if the clotting time was below this level.

Angiographic review and caliper assessment of the extent of coronary artery obstruction were performed by 2 experienced observers blinded with respect to pretreatment and clinical outcome. Hospital records of the

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TABLE I Clinical and Demographic Data

	Group A	Group B
Sex: M/F	26/9	17/1
Mean age (yrs)	52	60
Range	(39–66)	(39–76)
Recent acute myocardial infarction (%)	14 (40)	8 (44)
Unstable angina (%)	30 (85)	13 (72)
Prior thrombolytic therapy (>7 days) (%)	3 (8)	0
Antiplatelet therapy (%)	33 (94)	17 (94)
Intravenous nitroglycerin (%)	16 (46)	9 (50)

identified patients were reviewed for data regarding demographics, clinical presentation, in-hospital management, concomitant medications (including intravenous heparin and antiplatelet agents) and clinical outcome. PTCA outcome was assessed for angiographic success (defined as a final stenosis <50%), nonocclusive residual thrombus and occlusive thrombus at, or distal to, the PTCA site. Clinical outcome was examined with regard to the need for thrombolytic therapy, urgent coronary artery bypass grafting, myocardial infarction or a combination of these.

Statistical evaluation of group differences was performed using chi-square analysis or Fisher's exact test where appropriate. A p value <0.05 was considered statistically significant.

RESULTS

Fifty-three patients meeting the study criteria were identified. Clinical and demographic data are listed in Table I. Group A consisted of 35 patients who received continuous intravenous heparin from 1 to 7 days (mean 5.8, range 1 to 9) before PTCA while the 18 patients in group B received either no intravenous heparin (n = 17) or <24 hours (n = 1) of it. There were no significant group differences in patient age, frequency of recent infarction (>24 hours but <4 weeks), concomitant antiplatelet therapy (including aspirin), presence of unstable angina (rapidly progressive change in patient symptomatology or angina at rest without evidence of myocardial infarction) or requirement for intravenous nitroglycerin. All PTCA procedures were performed for persistent symptoms despite intensive, in-hospital medical regimens.

The angiographic features of each group were also comparable. There were no significant differences in the distribution or extent of significant (>70% diameter reduction) coronary disease. There were no differences in culprit vessel anatomy or severity of pre-PTCA stenosis (group A 86 ± 13% vs group B 84 ± 11%). Moreover, there were no differences in the presence of high risk features, such as bifurcation lesions (1 in group A, 0 in group B), stenosis length (no lesion in either group >10 mm) or angulated segments.

The indications for intravenous heparin therapy in the patients in group A were the presence of thrombus on the diagnostic coronary angiogram (22 patients), unstable angina (8 patients) and prior thrombolytic therapy (3 patients). The adequacy of systemic anticoagulation during the period of heparin infusion in 30 group A patients was verified from the hospital record. In all but one instance prolongation of the partial thromboplastin time was therapeutic (>1.5 × control) within 24 hours of the PTCA.

All PTCA procedures were performed in a standardized fashion by the same group of 4 staff angiographers over the time interval of this study. The frequency distribution of individual angiographers was unchanged over the time interval of the study and was similar for both groups of patients.

As seen in Figure 1, the uncomplicated angiographic success rate for the 35 patients in group A (94%) was significantly higher than for the 18 patients in group B (61%). One patient in group B had an unsuccessful outcome due to failure of the balloon-guidewire unit to cross the lesion. Residual nonocclusive thrombus was present in 6 patients in group A (17%) and 4 patients in group B (22%). This difference was not statistically significant.

Total vessel occlusion occurred in the catheterization laboratory in 2 patients in group A and 6 patients in

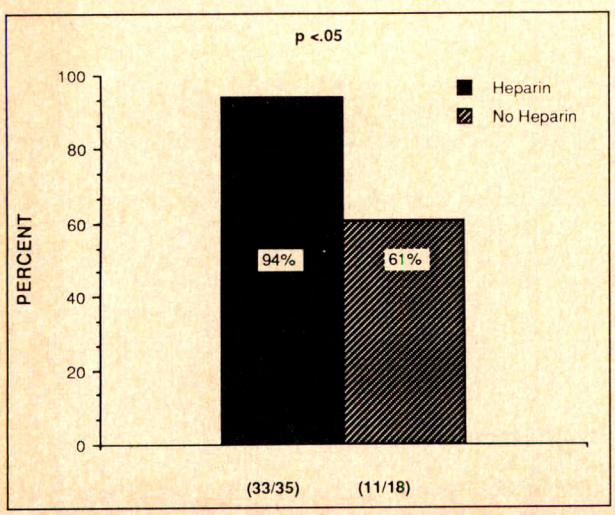


FIGURE 1. Statistically significant improvement in the angiographic result was noted in the group receiving heparin pretreatment.

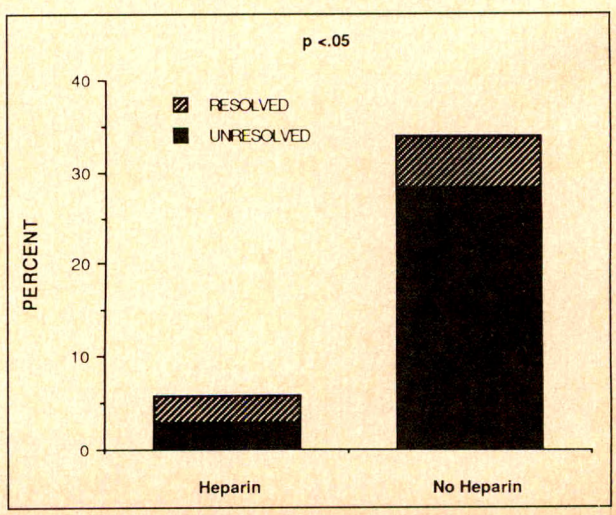


FIGURE 2. Complete (thrombotic) vessel occlusion occurred more frequently in the nonheparin-pretreated group (6 of 18 patients) than in the heparinized group (2 of 35 patients).

group B (Figure 2). Intracoronary streptokinase was given to both patients in group A (1 having received prior streptokinase therapy) and was successful in achieving reperfusion in 1. In group B (none received prior streptokinase) 2 patients received streptokinase with reperfusion achieved in 1. Despite attempts to reestablish flow using repeated dilatation, 4 of the 6 patients in group B had unresolved vessel closure resulting in ongoing myocardial ischemia and were taken emergently to the operating room. One patient in each group with unresolved occlusion was managed conservatively due to the absence of clinical or hemodynamic deterioration. Thus, in group A unresolved occlusion occurred with a frequency of 3% in contrast to 28% in group B ($p < 0.05$). It should be noted that no occlusion occurred primarily as the result of coronary dissection. There were no deaths in either group. Finally, it is emphasized that satisfactory prolongation of the activated clotting time (>300 seconds) was documented in all 8 patients with vessel occlusion.

In group A 5 PTCA procedures were performed immediately after the diagnostic catheterization with a successful result in 3 patients and acute closure in 2. In group B 10 PTCA procedures were performed immediately after the diagnostic study with success achieved in 7 patients and acute closure in 3. Thus, in this clinical setting, ad hoc PTCA carried a significantly lower success rate compared to the entire study population (ad hoc 67%, total population 85%, $p < 0.05$) and a higher risk of acute closure (ad hoc 33%, total population 15%, $p < 0.05$).

The fate of the intracoronary thrombus in those patients in whom serial coronary angiograms were available for review (31 in group A, 8 in group B) is of interest. There was a statistically significant increase in the frequency of clot propagation in group B (25 vs 13%, $p < 0.05$). Conversely, the frequency of improvement in appearance and size of the thrombus was significantly greater in group A (38 vs 0%, $p < 0.001$). Figure 3 shows this behavior in 1 such group A patient.

DISCUSSION

Improvements in instrumentation and pharmacologic therapy have been largely responsible for the expanded indications for PTCA over initial recommendations.[8,9] However, even with the advent of moveable guidewire systems a significant incidence of acute procedural complications persists.[3,10] Several preprocedural variables have been identified as factors that increase the risk of an unsuccessful outcome. Intracoronary thrombus has been shown to pose an increased risk to PTCA.[1–3] Although a decreased incidence of acute thromboembolic complications during PTCA has been associated with antiplatelet therapy,[11,12] no studies are available to date addressing the efficacy of such pretreatment in the setting of preprocedural thrombus. Preliminary uncontrolled studies of the efficacy of prolonged heparin infusion before PTCA in the setting of thrombus suggest that outcome may be improved.[4,5] A recently published study examining the incidence of thromboembolic complications in patients with intracoronary thrombus found no difference in clinical outcome in patients pretreated with heparin.[13] However, the inclusion of patients with a totally occluded vessel in that study confounds the interpretation of the data.

In the present retrospective study we noted a significant decrease in the immediate occlusive complications of PTCA in the setting of preexistent thrombus in the group receiving intravenous heparin for >24 hours. Interestingly, the occurrence of residual nonocclusive thrombus was unaffected by heparin pretreatment and may reflect the equal frequency of antiplatelet therapy in both groups. It should be emphasized that antiplatelet agents have not, by themselves, been shown to enhance the safety of PTCA in this unique clinical setting. Thus, we conclude that the addition of prolonged (>24 hours) intravenous heparin administration to the pre-PTCA treatment regimen confers additional benefit with respect to immediate outcome.

It should be noted that no significant bleeding complications occurred in group A, indicating no additional

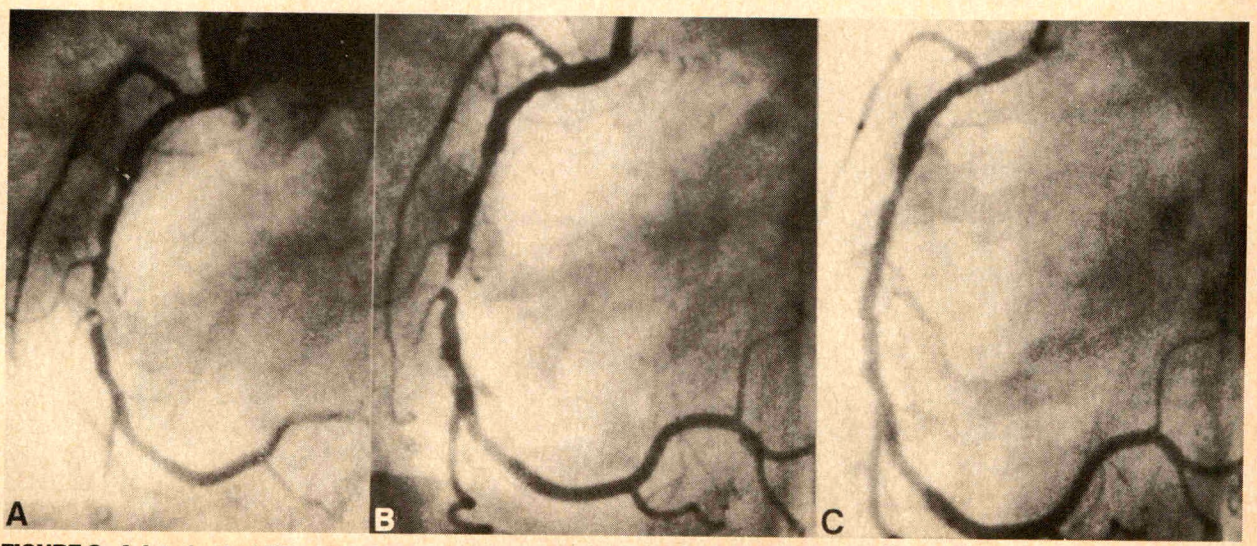


FIGURE 3. *A*, intraluminal filling defect superimposed on high-grade stenosis in the mid-right coronary artery. *B*, angiographic resolution of filling defect after 1 week of intravenous heparin therapy. *C*, immediate appearance of right coronary artery after PTCA.

risk to those patients treated with prolonged heparinization. In addition, only 1 PTCA in group A was performed before heparin therapy was administered for the desired duration. This supports the notion that prolonged heparin administration is an effective and safe adjunct to the management of patients with coronary thrombus.[14,15] However, it is recognized that not all patients with coronary thrombus can be expected to improve or remain clinically stable during prolonged heparin infusion.

The conclusions drawn herein need to be tempered in light of this study's retrospective nature. It should be emphasized that both patient groups were equally distributed over the time interval of the study. Coronary dilatation systems and pharmacologic regimens were unchanged over the time interval of the study. Decisions regarding the timing of PTCA and the institution and duration of heparin therapy were made by the referring physician on a case by case basis. Notably, over the time interval of the study there was no apparent consensus with respect to the appropriate management of these patients. In no patient was there an identifiable contraindication to long-term heparin therapy and, therefore, all patients were potentially suitable for such treatment. Our review indicated that the coronary anatomic data and modes of clinical presentation were similar in both groups. However, in this retrospective, noncontrolled study we acknowledge that important, albeit unidentified, variables or biases may exist.

All PTCA procedures were performed by the same staff angiographers over the time interval of the study. While individual decisions regarding management of acute vessel closure could not be properly controlled in a retrospective study, our observations regarding the disparity in immediate postprocedural coronary thrombotic occlusion remain valid and are clearly independent of subsequent management decisions.

The angiographic recognition of intracoronary thrombus is fraught with ambiguity. Our working definition, adopted from other investigators, is necessarily rigid and we recognize that our data represent an underestimation of the true frequency of coronary thrombus. Nevertheless, the primary endpoint of this study—vessel occlusion—was equally stringent and thus our conclusions remain clinically relevant.

In summary, prolonged intravenous heparin therapy appears to be beneficial in reducing the occlusive complications of PTCA in patients with preexistent coronary thrombus.

Acknowledgment: We would like to express our thanks to the members of the technical staff of the cardiac catheterization laboratories. In addition we acknowledge the expert secretarial assistance of Nedra Ellis.

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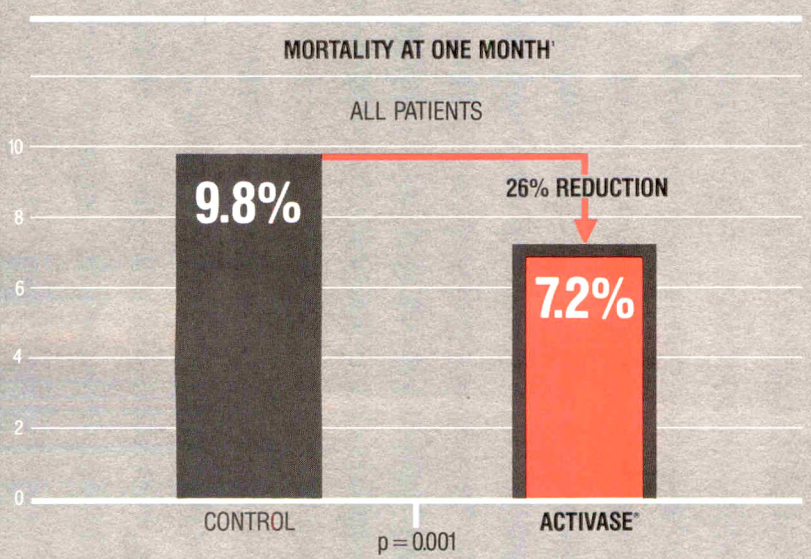
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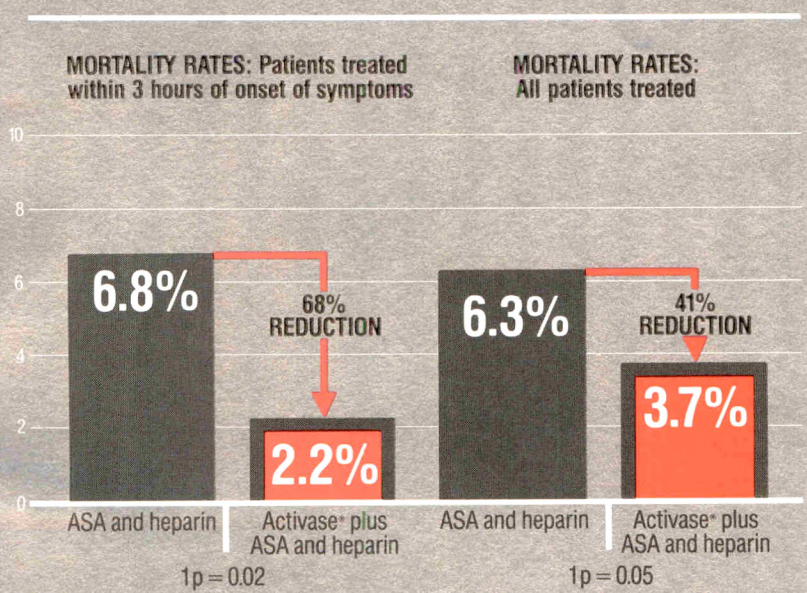
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††Although these data do not demonstrate unequivocally a significant reduction in mortality for this study, they do indicate a trend that is supported by the results of the ASSET study.

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Occurrence of stroke comparable to placebo

ACTIVASE®	PLACEBO
1.1%	**1.0%**

Data from the ASSET study (N = 5,013) reported the overall risk of post-MI stroke with Activase® (1.1%) was comparable to placebo (1.0%).[1]

Bleeding is the most common complication of thrombolytic therapy, with intracranial bleeding being the most serious. Activase® is contraindicated in patients with: active internal bleeding, history of cerebrovascular accident, recent (within two months) intracranial or intraspinal surgery or trauma, intracranial neoplasm, arteriovenous malformation, or aneurysm, known bleeding diathesis, severe uncontrolled hypertension. (See WARNINGS section of brief summary of prescribing information.)

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OPTIMIZE THERAPEUTIC BENEFITS THROUGH PROPER PATIENT SELECTION

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Therapeutic benefits in patients up to 75 years of age

Proven reduction in mortality in patients up to 75 years of age when used within 5 hours of acute MI onset[1]

Easy-to-follow dosing guidelines



Standard dose: 100 mg

For patients less than 65 kg: 1.25 mg/kg

Initiate lytic dose as follows: 60% of total therapeutic dose should be administered in the first hour of which 6-10 mg should be administered as bolus. The remaining 40% is delivered over the next 2 hours.

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Brief Summary
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INDICATIONS AND USAGE: ACTIVASE® is indicated for use in the management of acute myocardial infarction (AMI) in adults for the lysis of thrombi obstructing coronary arteries, the reduction of infarct size, the improvement of ventricular function following AMI, the reduction of the incidence of congestive heart failure and the reduction of mortality associated with AMI. Treatment should be initiated as soon as possible after the onset of AMI symptoms.

CONTRAINDICATIONS: Because thrombolytic therapy increases the risk of bleeding, ACTIVASE® is contraindicated in the following situations: • Active internal bleeding • History of cerebrovascular accident • Recent (within two months) intracranial or intraspinal surgery or trauma (see WARNINGS) • Intracranial neoplasm, arteriovenous malformation, or aneurysm • Known bleeding diathesis • Severe uncontrolled hypertension.

WARNINGS: Bleeding The most common complication encountered during ACTIVASE® therapy is bleeding. The type of bleeding associated with thrombolytic therapy can be divided into two broad categories: • Internal bleeding involving the gastrointestinal or genitourinary tract, or retroperitoneal or intracranial sites • Superficial or surface bleeding, observed mainly at invaded or disturbed sites (e.g., sites of venous cutdown, arterial puncture, recent surgical intervention).

Concomitant use of heparin anticoagulation may contribute to bleeding. Some hemorrhagic episodes occurred one or more days after the effects of ACTIVASE® had dissipated, but while heparin therapy was continuing.

As fibrin is lysed during ACTIVASE® therapy, bleeding from recent puncture sites may occur. Therefore, thrombolytic therapy requires careful attention to all potential bleeding sites (including sites of catheter insertion, arterial and venous puncture, cutdown and needle puncture).

Intramuscular injections and nonessential handling of the patient should be avoided during treatment with ACTIVASE®. Venipunctures should be performed carefully and only as required.

Should an arterial puncture be necessary during an infusion of ACTIVASE® it is preferable to use an upper extremity vessel accessible to manual compression. Pressure should be applied for at least 30 minutes, a pressure dressing applied and the puncture site checked frequently for evidence of bleeding.

Should serious bleeding (not controllable by local pressure) occur, the infusion of ACTIVASE® and any concomitant heparin should be terminated immediately.

Each patient being considered for therapy with ACTIVASE® should be carefully evaluated and anticipated benefits weighed against potential risks associated with therapy.

In the following conditions, the risks of ACTIVASE® therapy may be increased and should be weighed against the anticipated benefits: • Recent (within 10 days) major surgery, obstetrical delivery, organ biopsy, previous puncture of noncompressible vessels • Cerebrovascular disease • Recent (within 10 days) gastrointestinal or genitourinary bleeding • Recent (within 10 days) trauma • Hypertension: systolic BP≥180 mm Hg and/or diastolic BP≥110 mm Hg • High likelihood of left heart thrombus, e.g., mitral stenosis with atrial fibrillation • Acute pericarditis • Subacute bacterial endocarditis • Hemostatic defects including those secondary to severe hepatic or renal disease • Significant liver dysfunction • Pregnancy • Diabetic hemorrhagic retinopathy, or other hemorrhagic ophthalmic conditions • Septic thrombophlebitis or occluded AV cannula at seriously infected site • Advanced age, i.e., over 75 years old • Patients currently receiving oral anticoagulants • Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location.

Arrhythmias Coronary thrombolysis may result in arrhythmias associated with reperfusion. These arrhythmias are not different from those often seen in the ordinary course of AMI and may be managed with standard antiarrhythmic measures. It is recommended that antiarrhythmic therapy for bradycardia and/or ventricular irritability be available when infusions of ACTIVASE® are administered.

PRECAUTIONS: General Standard management of MI should be implemented concomitantly with ACTIVASE® treatment. Noncompressible arterial puncture must be avoided. Arterial and venous punctures should be minimized. In the event of serious bleeding, ACTIVASE® and heparin should be discontinued immediately. Heparin effects can be reversed by protamine.

Readministration There is no experience with readministration of ACTIVASE®. If anaphylactoid reaction occurs, infusion should be discontinued immediately and appropriate therapy initiated.

Although sustained antibody formation in patients receiving one dose of ACTIVASE® has not been documented, readministration should be undertaken with caution.

Laboratory Tests During ACTIVASE® therapy, results of coagulation tests and/or measures of fibrinolytic activity may be unreliable unless specific precautions are taken to prevent *in vitro* artifacts. ACTIVASE® is an enzyme that when present in blood in pharmacologic concentrations remains active under *in vitro* conditions. This can lead to degradation of fibrinogen in blood samples removed for analysis. Collection of blood samples in the presence of aprotinin (150-200 units/mL) can to some extent mitigate this phenomenon.

Drug Interactions The interaction of ACTIVASE® with other cardioactive drugs has not been studied. In addition to bleeding associated with heparin and vitamin K antagonists, drugs that alter platelet function may increase the risk of bleeding if administered prior to, during or after ACTIVASE® therapy.

Use of Anticoagulants Heparin has been administered concomitantly with and following infusions of ACTIVASE® to reduce the risk of rethrombosis. Because either heparin or ACTIVASE® alone may cause bleeding complications, careful monitoring for bleeding is advised, especially at arterial puncture sites.

Pregnancy (Category C) Animal reproduction studies have not been conducted with ACTIVASE®. It is also not known whether ACTIVASE® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ACTIVASE® should be given to a pregnant woman only if clearly needed.

Pediatric Use Safety and effectiveness of ACTIVASE® in children has not been established.

Carcinogenesis, Mutagenesis, Impairment of Fertility Long-term studies in animals have not been performed to evaluate the carcinogenic potential or the effect on fertility. Short-term studies, which evaluated tumorigenicity of ACTIVASE® and effect on tumor metastases in rodents, were negative.

Studies to determine mutagenicity (Ames test) and chromosomal aberration assays in human lymphocytes were negative at all concentrations tested. Cytotoxicity, as reflected by a decrease in mitotic index, was evidenced only after prolonged exposure and only at the highest concentrations tested.

Nursing Mothers It is not known whether ACTIVASE® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ACTIVASE® is administered to a nursing woman.

ADVERSE REACTIONS: Bleeding The most frequent adverse reaction associated with ACTIVASE® is bleeding. The type of bleeding associated with thrombolytic therapy can be divided into two broad categories: • Internal bleeding involving the gastrointestinal or genitourinary tract, or retroperitoneal or intracranial sites • Superficial or surface bleeding, observed mainly at invaded or disturbed sites (e.g., sites of venous cutdown, arterial puncture, recent surgical intervention).

The following incidence of significant internal bleeding (estimated as>250 cc blood loss) has been reported in studies in over 800 patients treated at all doses:

	Total Dose ≤ 100 mg	Total Dose > 100 mg
gastrointestinal	5%	5%
genitourinary	4%	4%
ecchymosis	1%	<1%
retroperitoneal	<1%	<1%
epistaxis	<1%	<1%
gingival	<1%	<1%

The incidence of intracranial bleeding in patients treated with ACTIVASE® Alteplase, recombinant, is as follows:

Dose	Number of Patients	%
100 mg	3272	0.4
150 mg	1779	1.3
1-1.4 mg/kg	237	0.4

These data indicate that a dose of 150 mg of ACTIVASE® should not be used because it has been associated with an increase in intracranial bleeding.

Recent data indicate that the incidence of stroke in 6 randomized double-blind placebo controlled trials[1-7] is not signficantly different in the ACTIVASE® treated patients compared to those treated with placebo (37/3161, 1.2% versus 27/3092, 0.9%, respectively) (p = 0.26).

Should serious bleeding in a critical location (intracranial, gastrointestinal, retroperitoneal, pericardial) occur, ACTIVASE® therapy should be discontinued immediately, along with any concomitant therapy with heparin.

Fibrin, which is part of the hemostatic plug formed at needle puncture sites, will be lysed during ACTIVASE® therapy. Therefore, ACTIVASE® therapy requires careful attention to potential bleeding sites.

Allergic Reactions No serious or life-threatening allergic reactions have been reported. Other mild hypersensitivity reactions such as urticaria have been observed occasionally.

Other Adverse Reactions Other adverse reactions have been reported, principally nausea and/or vomiting, hypotension, and fever. These reactions are frequent sequelae of MI and may or may not be attributable to ACTIVASE® therapy.

DOSAGE AND ADMINISTRATION: Administer ACTIVASE® as soon as possible after the onset of symptoms.

ACTIVASE® is for intravenous administration only.

The recommended dose is 100 mg administered as 60 mg (34.8 million IU) in the first hour (of which 6 to 10 mg is administered as a bolus over the first 1-2 minutes), 20 mg (11.6 million IU) over the second hour, and 20 mg (11.6 million IU) over the third hour. For smaller patients (less than 65 kg), a dose of 1.25 mg/kg administered over 3 hours, as described above, may be used.[8]

A DOSE OF 150 MG OF ACTIVASE® SHOULD NOT BE USED BECAUSE IT HAS BEEN ASSOCIATED WITH AN INCREASE IN INTRACRANIAL BLEEDING.

Although the use of anticoagulants and antiplatelet drugs during and following administration of ACTIVASE® has not been shown to be of unequivocal benefit, heparin has been administered concomitantly for 24 hours or longer in more than 90% of patients. Aspirin and/or dipyridamole have been given either during and/or following heparin treatment.

Reconstitution and Dilution DO NOT USE IF VACUUM IS NOT PRESENT.

ACTIVASE® should be reconstituted by aseptically adding the appropriate volume of the accompanying Sterile Water for Injection, USP to the vial. It is important that ACTIVASE® be reconstituted only with Sterile Water for Injection, USP, without preservatives. Do not use Bacteriostatic Water for Injection, USP. The reconstituted preparation results in a colorless to pale yellow transparent solution containing ACTIVASE® 1.0 mg/mL at approximately pH 7.3. The osmolality of this solution is approximately 215 mOsm/kg.

Because ACTIVASE® contains no antibacterial preservatives, it should be reconstituted immediately before use. The solution may be used for intravenous administration within 8 hours following reconstitution when stored between 2-30°C. Before further dilution or administration, the product should be visually inspected for particulate matter and discoloration prior to administration whenever solution and container permit.

ACTIVASE® is stable for up to 8 hours in these solutions at room temperature. Exposure to light has no effect on the stability of these solutions. Excessive agitation during dilution should be avoided; mixing should be accomplished with gentle swirling and/or slow inversion. Do not use other infusion solutions, e.g., Sterile Water for Injection, USP or preservative-containing solutions for further dilution.

No other medication should be added to infusion solutions containing ACTIVASE®. Any unused infusion solution should be discarded.

HOW SUPPLIED: ACTIVASE® is supplied as a sterile, lyophilized powder in 20 mg and 50 mg vials containing vacuum, each packaged with diluent for reconstitution.

Storage Store lyophilized ACTIVASE® at controlled room temperature not to exceed 30°C (86°F), or under refrigeration (2-8°C/36-46°F). Protect the lyophilized material during extended storage from excessive exposure to light.

Do not use beyond the expiration date stamped on the vial.

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Manufactured by
GENENTECH®, INC.
460 Point San Bruno Blvd.
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April, 1989

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Changing Use of Coronary Angioplasty and Coronary Bypass Surgery in the Treatment of Chronic Coronary Artery Disease

William S. Weintraub, MD, Ellis L. Jones, MD, Spencer B. King, III, MD, Joseph Craver, MD, John S. Douglas, Jr., MD, Robert Guyton, MD, Henry Liberman, MD, and Douglas Morris, MD

Changes in the use of coronary artery bypass grafting (CABG) and percutaneous transluminal coronary angioplasty (PTCA) over the last several years have resulted in a new and different environment for the interventional treatment of coronary artery disease. This study explores these changes as applied to the treatment of chronic coronary artery disease. The study population comprised 14,078 patients undergoing diagnostic cardiac catheterization between 1981 and 1988. In 1981, 1,704 patients underwent a first known cardiac catheterization at Emory University Hospital or Crawford W. Long Hospital and were found to have significant coronary artery disease. Of these patients, 51.7% were treated medically, 44.0% by CABG and 4.3% with PTCA. A similar group comprised 1,719 patients in 1988. Of this group 41.2% were treated medically, 28.5% with CABG and 30.3% with PTCA. The data reveal a much more complex phenomenon than a simple increase in PTCA for the treatment of coronary disease at the expense of CABG. The CABG group aged such that the percent of the CABG population more than 65 years old increased from 26.0% of the total in 1981 to 44.9% of the total in 1988. The percent of patients with ejection fractions <50% in the CABG population increased from 24.5% in 1981 to 29.7% in 1988. The PTCA population had less severe disease, was younger and had better left ventricular function. Nonetheless, the percent more than 65 years old increased from 15.4% in 1981 to 35.4% in 1988. The percent of patients with ejection fractions <50% increased from 9.6% in 1981 to 15.1% in 1988. Similar changes were noted in the medically treated group. Not surprisingly, the biggest increases in PTCA occurred in 1- and 2-vessel disease patients, with a concomitant decrease in the CABG referrals in these patients. Thus, 2 processes occurred at the same time. The population grew older and had more significant coronary narrowing. At the same time PTCA was used with increasing frequency as a treatment for 1- and 2-vessel coronary artery disease. This has resulted in a marked shift in the CABG population. These changes have significant implications for policy planners, reimbursors and clinical researchers in the treatment of coronary artery disease.

(Am J Cardiol 1990;65:183–188)

The last several years have been a time of considerable change in the practice of cardiovascular medicine. The 1970s was a period of growth for coronary artery bypass grafting (CABG)[1] with a concomitant decrease in its complication rate.[2] Major studies during this period gradually defined the role of CABG. The introduction of percutaneous transluminal coronary angioplasty (PTCA) in the late 1970s has altered the treatment of coronary disease, and now there is uncertainty as to the respective roles of these techniques.[3–5] Furthermore, the demographic characteristics of the patient population that undergoes PTCA have also changed as the procedure has developed. Part of defining the place of CABG and PTCA is to understand the nature of the populations that undergo these procedures. Thus, the present study explores the changes that have occurred in the referral patterns to interventional cardiovascular procedures after diagnostic cardiac catheterization between 1981 and 1988 at 2 Emory University hospitals.

METHODS

Patient population: The population is drawn from patients undergoing initial diagnostic cardiac catheterization at Emory University Hospital or Crawford W. Long Hospital between 1981 and 1988. The catheterizations were performed to define the presence and extent of coronary artery disease. Patients undergoing coronary angioplasty for evaluation of acute myocardial infarction, valvular heart disease, congenital heart disease and primary myocardial diseases were excluded. Patients were considered to be referred to PTCA if it was performed within 30 days of the diagnostic catheterization. Patients were similarly considered to be referred to CABG if they had CABG within 30 days of the diagnostic catheterization and did not have an intervening PTCA. However, 1986 was the last full year before a prospective randomized trial of CABG and PTCA for the treatment of multivessel coronary disease began at Emory. The study population comprised 14,078 patients having a first known catheterization and found to have coronary disease between the years 1981 and 1988.

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TABLE I Total Study Population

Year	1981	1982	1983	1984	1985	1986	1987	1988	p Value
Number	1,704	1,803	1,788	1,526	1,931	1,742	1,865	1,719	
Ages (yrs)	58 ± 9	58 ± 10	59 ± 10	60 ± 11	56 ± 12	58 ± 12	61 ± 11	61 ± 11	<0.0001
% ≥65 years	23.9	29.0	32.0	35.0	27.4	32.0	40.6	40.6	<0.0001
% ≥75 years	2.6	4.0	5.1	6.4	5.6	8.1	9.4	10.6	<0.0001
% female	19.8	19.7	22.8	23.8	22.5	26.3	26.9	28.5	<0.0001
% class III/IV angina	56.5	42.1	54.6	55.8	64.5	67.9	67.2	60.2	0.05
1-vessel disease	627	682	628	569	827	690	692	692	0.02
2-vessel disease	506	516	578	470	569	550	574	528	
3-vessel disease	474	482	478	400	424	411	491	405	
Left main disease	100	123	104	87	111	91	108	94	
LVEF (%)	58 ± 16	59 ± 15	58 ± 16	56 ± 15	53 ± 12	54 ± 13	55 ± 14	56 ± 15	0.004
% LVEF <50%	30.0	24.6	28.1	29.0	27.6	30.2	31.8	28.3	NS

LVEF = left ventricular ejection fraction; NS = difference not significant.

TABLE II Medically Treated Patients

Year	1981	1982	1983	1984	1985	1986	1987	1988	p Value
Number	881	897	869	716	900	772	827	709	
Age (yrs)	57 ± 10	57 ± 10	58 ± 11	59 ± 11	56 ± 12	59 ± 11	61 ± 11	61 ± 11	<0.0001
% ≥65 years	22.5	24.4	26.0	34.0	26.4	32.5	41.7	41.5	<0.0001
% ≥75 years	3.3	4.2	4.6	6.5	5.9	7.5	10.2	11.8	<0.0001
% female	20.0	19.7	23.8	27.5	25.0	26.0	28.7	29.2	<0.0001
% class III/IV angina	47.8	33.0	47.4	53.1	60.8	65.9	61.7	54.8	0.015
1-vessel disease	441	497	457	390	472	371	388	345	NS
2-vessel disease	257	262	263	203	264	251	269	209	
3-vessel disease	165	126	140	117	147	139	154	136	
Left main disease	18	15	9	6	17	11	16	19	
LVEF (%)	55 ± 17	58 ± 16	55 ± 16	54 ± 15	53 ± 13	53 ± 14	53 ± 16	53 ± 16	0.004
% LVEF <50%	36.7	27.6	35.2	30.9	33.4	36.8	37.6	36.6	NS
Percent of Total Study Population Medically Treated									
Overall	51.7	49.8	48.6	46.9	46.6	44.3	44.3	41.2	
1-vessel disease	70.7	72.4	72.8	68.5	57.1	53.8	56.1	49.9	
2-vessel disease	50.8	50.8	45.5	43.2	46.4	45.6	46.9	39.6	
3-vessel disease	34.8	26.1	29.3	29.3	34.7	33.8	31.4	33.6	
Left main disease	18.0	12.2	8.7	6.9	15.3	12.1	14.8	20.2	

Abbreviations as in Table I.

TABLE III CABG Patients

Year	1981	1982	1983	1984	1985	1986	1987	1988	p Value
Number	749	811	787	672	561	508	568	490	
Age (yrs)	59 ± 9	60 ± 9	60 ± 10	61 ± 10	61 ± 10	62 ± 10	62 ± 10	62 ± 11	<0.0001
% ≥65 years	26.0	34.4	37.2	37.8	41.2	45.5	45.5	44.9	<0.0001
% ≥75 years	2.1	4.1	5.3	7.4	8.2	12.6	9.0	11.2	<0.0001
% female	18.6	19.4	21.9	18.3	20.0	22.6	23.8	25.7	0.003
% class III/IV angina	65.8	51.9	61.00	58.6	68.8	69.4	71.6	63.8	NS
1-vessel disease	114	114	77	80	42	34	34	29	<0.0001
2-vessel disease	244	234	280	231	167	149	156	160	
3-vessel disease	309	355	335	280	259	246	286	226	
Left main disease	82	108	95	81	93	79	92	75	
LVEF (%)	60 ± 15	60 ± 15	60 ± 15	57 ± 15	53 ± 12	53 ± 15	54 ± 14	56 ± 16	<0.0001
% LVEF <50%	24.1	22.4	23.2	30.3	30.1	35.2	34.4	29.7	0.03
% mortality	2.1	2.3	2.2	2.1	2.5	4.5	3.9	3.7	0.11
Percent of Total Study Population Treated by CABG									
Overall	44.0	45.0	44.0	44.0	29.1	29.2	30.5	28.5	
1-vessel disease	18.3	16.7	12.3	14.1	5.1	14.9	4.9	4.2	
2-vessel disease	48.2	46.3	48.4	49.1	29.3	27.1	27.2	30.3	
3-vessel disease	65.0	73.7	70.1	70.0	61.1	59.9	58.2	55.8	
Left main disease	82.0	87.8	91.3	93.1	83.8	86.8	85.2	79.8	

Abbreviations as in Table I.

Referral patterns to revascularization procedures were studied in these patients.

Cardiac catheterization: Coronary arteriography was performed in multiple right and left anterior oblique projections. All angiograms were interpreted by at least 2 angiographers. In classifying patients according to number of diseased vessels, a significant coronary lesion was defined as a ≥50% luminal diameter narrowing judged as an average of multiple views. Two- and 3-vessel disease was defined as the occurrence of such lesions in 2 or 3 of the major arterial systems. Contrast left ventriculograms were performed in the 30° right anterior oblique projection. Ejection fractions were calculated in 13,212 patients according to the area-length method.[6]

Angioplasty technique: All procedures were performed using standard techniques that have previously been described in detail.[7] Procedures were done by the femoral approach after sedation with diazepam 5 to 10 mg intravenously. Patients received aspirin 325 mg orally the night before the procedure and heparin 10 to 20,000 U intravenously during the procedure. Nifedipine 10 mg orally was administered in most patients and atropine 0.4 mg intravenously as required. Dilatation was performed using fixed wire balloon catheters (USCI Inc.) from 1981 to 1983, and various steerable catheter systems since 1983. Patients were treated after the procedure with aspirin and discharged after 1 to 3 days. Pre- and post-PTCA angiograms were measured by experienced angiographers (excluding the PTCA operator) and diameter stenosis results were calculated as the mean of 2 near orthogonal views using electronic calipers.

Bypass technique: CABG was performed with standard techniques. Myocardial protection is accomplished with hypothermia and crystalloid cardioplegia. Grafts were created from either the internal mammary arteries or vein grafts. When possible, patients were extubated the day after surgery and patients without complications were discharged after 6 to 9 days.

Data analysis: All data were complete except for some missing data on age, ejection fraction and angina class. Age was missing in 686 patients (4.9%), distributed as 648 (9.9%) in the medical group, 1 (0.1) in the CABG group and 37 (1.6%) in the PTCA group. The ejection fraction was missing in 866 patients (6.2%), distributed as 388 (5.9%) in the medical group, 262 (5.1%) in the CABG group and 216 (9.1%) in the PTCA group. Angina class was missing in 3,277 patients (23%), distributed as 1,749 (26.6%) in the medical group, 777 (15.1%) in the CABG group and 751 (31.8%) in the PTCA group. These data would have been available at the time of choice of therapy except for patients not having venticulograms. All data were prospectively entered into a computerized database. Data were displayed as raw counts, percents and mean ± standard deviation where appropriate. Categorical variables were compared by chi-square, and continuous variables by 1-way analysis of variance and unpaired tests. Significance testing compared data from 1981 to 1988, and also data across the 3 treatment groups. This was done to diminish the influence of interval variations over time. Statistical testing was done with BMDP.

RESULTS

From 1981 through 1988 the total population of patients undergoing cardiac catheterization to evaluate the presence or extent of coronary artery disease increased from 3,430 to 5,575 (Figure 1). The total undergoing CABG (patients catheterized within this institution and those referred after catheterization elsewhere) decreased from 1,732 to 1,404 while the total undergoing PTCA increased from 503 to 2,116. From the pool of patients undergoing angiography, we have studied the in-hospital referrals of patients with coronary artery disease to initial medical therapy, PTCA and CABG over these 8 years.

The total number of patients in the study population, mean age, percent ≥65 and ≥75 years old, percent female, number of patients with 1-, 2- and 3-vessel and left main disease, mean ejection fraction and percent with ejection fractions <50% are listed in Table I. There was an increase in age from 58 ± 9 to 61 ± 11 years ($p < 0.0001$) and the percent of patients over the age of 65 and over 75 years changed dramatically. There was also an increase in the percent of women. There was a slight decrease in mean ejection fraction (58 ± 16 to 56 ± 15%) ($p = 0.004$) over the 8 years. Surprisingly, there was a slight shift to fewer diseased

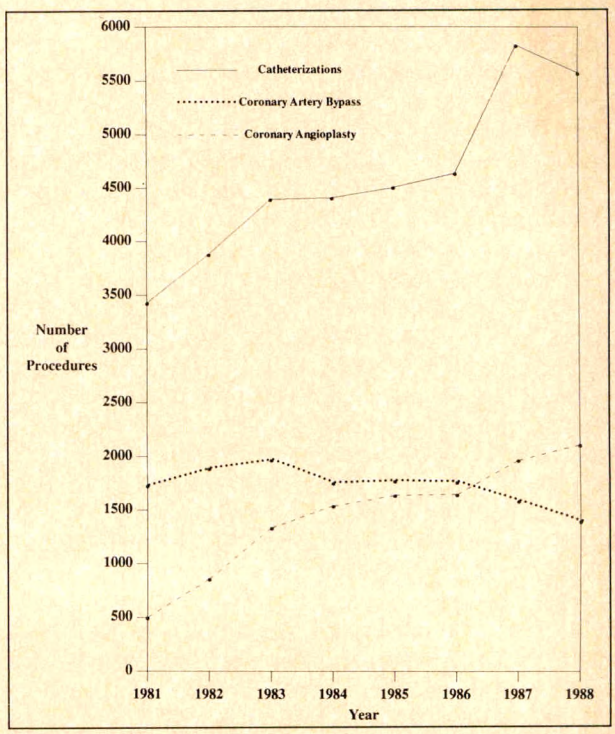


FIGURE 1. Patients undergoing cardiac catheterization, coronary artery bypass surgery and percutaneous transluminal angioplasty at Emory University Hospital and Crawford W. Long Hospital between 1981 and 1988. Data presented refer to the total population, of which the study population is a subset.

TABLE IV PTCA Patients

Year	1981	1982	1983	1984	1985	1986	1987	1988	p Value
Number	74	95	132	138	470	462	470	520	
Age (yrs)	56 ± 9	55 ± 10	55 ± 12	58 ± 11	50 ± 12	51 ± 13	59 ± 12	59 ± 12	0.01
% ≥65 years	15.4	15.9	29.3	26.3	12.6	16.3	32.6	35.4	0.001
% ≥75 years	2.1	4.1	5.3	7.4	8.2	12.6	9.0	11.2	<0.03
% female	31.1	23.2	21.2	31.2	20.6	31.0	27.7	30.2	NS
% class III/IV angina	54.8	32.8	57.4	53.6	64.6	69.8	70.6	64.4	NS
1-vessel disease	69	74	94	99	313	285	270	318	<0.0001
2-vessel disease	5	20	35	36	138	150	149	159	
3-vessel disease	0	1	3	3	18	26	51	43	
Left main disease	0	0	0	0	1	1	0	0	
LVEF (%)	67 ± 12	63 ± 13	65 ± 11	62 ± 12	57 ± 9	58 ± 9	60 ± 11	61 ± 13	0.0002
% LVEF <50%	9.6	13.8	11.0	12.9	12.6	13.7	17.7	15.1	NS
% mortality	0	0	0.8	0	0.6	0.4	0.6	0.8	NS
% CABG	27.0	9.5	9.1	10.9	8.7	4.8	5.3	5.8	<0.0001
Percent of Total Study Population Treated by PTCA									
Overall	4.3	5.3	7.4	9.0	24.3	26.5	25.2	30.3	
1-vessel disease	11.1	10.9	15.0	17.4	37.8	41.3	39.0	46.0	
2-vessel disease	1.0	3.9	6.1	7.7	24.3	27.3	26.0	30.1	
3-vessel disease	0	0.2	0.6	0.8	4.2	6.3	10.4	10.6	
Left main disease	0	0	0	0	0.9	1.1	0	0	

Abbreviations as in Table I.

vessels. Thus, changes in referral patterns must be seen against a background of a changing, and in particular, an aging patient population.

The patients treated medically are listed in Table II. The number of patients treated medically decreased from 881 to 709. The mean age increased from 57 ± 10 to 61 ± 11 years ($p < 0.0001$). The distribution of number of diseased vessels was unchanged. The mean ejection fraction of these patients decreased slightly from 55 ± 17 to 53 ± 16% ($p = 0.004$). The percent of patients treated medically decreased consistently over the entire study period. However, the percent of medically treated patients decreased from 70.7 to 49.9% in the 1-vessel disease group, while it was essentially unchanged in the 3-vessel disease group.

Similar data for the CABG patients are listed in Table III. The total number of patients internally referred decreased from 749 to 490. The mean age increased from 59 ± 9 to 62 ± 11 years ($p < 0.0001$). The percent of patients ≥65 years increased from 26.0 to 44.9% ($p < 0.0001$). A similar increase was noted in patients ≥75 years old. The mean ejection fraction decreased from 60 ± 15 to 56 ± 16% ($p < 0.0001$). The percent of patients with ejection fractions <50 increased from 24.1 to 29.7% ($p < 0.0001$). The percent of the total population referred to CABG decreased from 44.0 to 28.5%. CABG referrals dropped for each subgroup of patients as defined by number of diseased vessels, except for left main disease. For 1-vessel disease referral to CABG has become relatively rare, decreasing from 18.3% of the total population in 1981 to 4.2% in 1988. The referrals of patients with 3-vessel disease decreased modestly from 65.0 to 55.8%.

Data concerning the use of PTCA are listed in Table IV. The number of internal referral patients increased more than 7-fold from 74 in 1981 to 520 in 1988. The age also increased from 56 ± 9 to 59 ± 12 years ($p = 0.008$). The percent ≥65 years old increased from 15.4 to 35.4% ($p = 0.001$). There was a similar increase in patients ≥75 years old. The ejection fraction decreased from 66 ± 12 to 61 ± 13% ($p = 0.002$). The overall percent of the total population referred to PTCA increased from 4.3 to 30.3%. The percent increase in referrals with 1-, 2- and 3-vessel disease has mirrored the decrease in CABG referrals and decreased use of medical therapy without revascularization. For 1-vessel disease, PTCA referrals increased from 69 (11.1% of the population) to 318 (46.0% of the population). For 2-vessel disease PTCA referrals increased from 5 (1.0%) to 139 (30.1%) patients. Although over time more severely diseased patients underwent PTCA, the percent of patients requiring CABG after failed angioplasty actually decreased ($p < 0.0001$). The ejection fractions have remained higher ($p < 0.0001$), the vessels less severely diseased ($p < 0.0001$) and the ages lower ($p < 0.0001$) for the PTCA compared to the CABG patients throughout. The percent of women was greater for PTCA than for CABG ($p < 0.0001$), although this was not true in every year of the study. There was no significant difference in angina class between PTCA and CABG patients, although there were more class III and class IV angina patients in the intervention groups than in the medical group. The increase in PTCA for multivessel disease in 1987 and 1988 may be due, in part, to the randomized trial comparing coronary surgery to PTCA.

Mortality data from this study must be compared to other studies with caution because the patients were only assigned to an intervention group if they had that form of therapy within 30 days. This may lead to higher mortality rates than in patients in whom medical therapy is tried initially. There were 143 deaths (2.8%) in the surgical group between 1981 and 1988. Postoperative death correlated with increased age, female gender, left

main coronary disease and ejection fraction <50%. The mortality was 1.5% <65 and 4.8% ≥65 years of age ($p < 0.0001$). The mortality was 2.0% for men and 5.6% for women ($p < 0.0001$). The mortality was 2.4% for 1- to 3-vessel disease and 5.2% for left main disease ($p < 0.0001$). The mortality was 1.8% for ejection fractions ≥50% and 4.3% for ejection fractions <50% ($p < 0.0001$). Operative mortality increased from 2.1% in 1981 to 3.7% by 1988, but these changes could be explained entirely by the changes in the population over this period. Thus, for patients under age 65 with 1- to 3-vessel disease and ejection fractions >50% there were 3 deaths among 359 (0.8%) patients in 1981, and 1 in 167 (0.6%) patients in 1988. This low risk group comprised 50.6% of the patients in 1981, but decreased to 35.4% in 1988. There were 13 (0.6%) deaths in the PTCA population. Mortality after PTCA was 0.3% for patients with ejection fractions ≥50% and 1.6% for patients with ejection fractions <50% ($p = 0.003$). Mortality after PTCA was 0.3% for 1-vessel disease and 1.5% for multivessel disease ($p = 0.001$). Mortality was 0% in 1981 and 0.8% in 1988 (difference not significant).

DISCUSSION

We present data that reveal several things about the practice of cardiology in a tertiary care center. First, the age of the population has increased and the left ventricular function has deteriorated. Second, PTCA has begun to mature as a treatment for coronary disease, and is even being used with increasing frequency to treat multivessel disease. This has begun to change the CABG referral base because patients who have less severe disease and better left ventricular function are being selected for PTCA. These trends were well established by the end of 1986 before the beginning of the randomized trial comparing CABG to PTCA. Thus, the maturation process of PTCA has resulted in more patients undergoing this procedure and fewer patients being treated medically or by CABG. This change in pattern may increase the complication rates for both procedures. In addition, both the CABG and PTCA populations have been maintained through referrals from outside catheterization laboratories. This has created a parallel system of referral for CABG and PTCA.

National trends can be determined from discharge data compiled by the National Center for Health Statistics. In 1982 there were 170,000 CABG procedures.[8] This increased to 202,000 in 1984[9] and to 284,000 in 1986.[10] In 1984 35% of patients were over 65 years of age, and in 1986 44% were over 65. PTCA data were first available for the year 1983 when 32,300 procedures were performed.[11] This increased to 46,000 in 1984[9] and to 133,000 in 1986.[10] In 1984 26% of the patients were over 65 years of age and in 1986 33% were over 65. These data represent discharge data for nonfederal hospitals in the United States. Procedures were determined from ICD-9-CM codes. Nationally there has been a steady increase in CABG, while the growth in PTCA has been relatively faster. Available data suggest that PTCA has not been as widely applied as CABG, suggesting that the trend toward more PTCA and less CABG is not as firmly established nationally as it is at Emory. The national trend toward performing these procedures on an increasing percentage of patients over 65 years old is virtually identical to that at Emory both for CABG and PTCA. In addition to these data, the National Heart, Lung, and Blood Institute's PTCA Registry showed an increase in age, an increase in patients with abnormal ejection fractions and an increase in multivessel disease patients from the 1977 to 1981 cohort to the 1985 to 1986 cohort.[12] While increasing use of PTCA is clear, the national impact of PTCA on CABG is less certain.

The value of PTCA in the treatment of angina pectoris has been established[13,14] although the use of PTCA in preventing myocardial infarction and prolonging life remains speculative. Current data suggest that patients have a good prognosis after PTCA,[14–16] although comparisons to CABG are just beginning. Most CABG patients have multivessel disease, are increasingly elderly and have compromised left ventricular function. Routine care for such sick patients poses a tremendous challenge to the cardiovascular surgeon and supporting staff. While patients referred to PTCA have less serious disease, there is increasing use of PTCA in patients with 2- and even 3-vessel disease. Whether there really is uncertainty as to the correct form of therapy for many patients cannot easily be gleaned from this study, however. It is possible that the sicker patients with multivessel disease and more threatened left ventricular myocardium or with more diffuse disease are being appropriately referred to CABG. Alternatively, the multivessel disease patients sent to PTCA may be appropriately selected based on anatomic factors that allow PTCA to be performed safely. In addition, there may be patients sent to PTCA who are judged to be "inoperable" for CABG ("salvage PTCA"). Thus, it is possible that at any point in time there is either a large or a small pool of patients who could have either procedure. This itself is a crucial issue. If the pool of patients who could have either procedure is relatively large, then the need for trials to determine which procedure offers better revascularization and which procedure offers the better or more efficient long-term results are far more crucial than if the pool is small.

Selection of therapy is based on value as perceived by the clinician and the patient, and this perceived value may encompass many factors. The factors that the physician should be assessing include decreased symptoms, improved prognosis at minimum cost, decreased mortality and decreased morbidity. Prognosis includes the risk of future cardiac events and the need for repeat procedures as well as risk of death. Cost refers to total direct and indirect costs, not simply in-hospital charges. The most cost-effective form of therapy in the overlapping pool of patients cannot be defined without prospective trials, because it is not possible to establish relative values due to uncertainty concerning selection of therapy. Pending the results of such trials, the increasing use of PTCA must be explained on the basis of a perception of increased value relative to medical therapy or CABG in certain patient subsets. It could also be related to

increased familiarity with the technique on the part of the referring physicians and PTCA operators. Physicians may also respond to evidence based on accumulated experience that PTCA is worthwhile. There have also been technical changes, such as the introduction of the steerable catheter in 1983[17] and many subsequent innovations, which may expand the scope of patients for whom the physician perceives PTCA is worthwhile. Thus, it is clear that both the population and the techniques are changing, making comparisons between techniques difficult.

The potential populations for CABG and PTCA are unlikely to overlap completely. PTCA remains relatively ineffective in diffuse disease, chronic total occlusions and left main disease. For studies aimed at examining the relative roles of the 2 procedures, it is essential to have a firm understanding of the population from which the patients are drawn. If the population in the study is composed of a small fraction of the less ill patients with multivessel disease, the ability to generalize results will be much less than if the population is drawn from a wider spectrum. Thus, the value of CABG and PTCA can best be ascertained as part of a large database of all patients having either procedure, including a randomized group in whom there is felt to be potential overlap of the 2 techniques. Thus, the randomized trials will provide necessary data to define the cost effectiveness of PTCA versus CABG in overlapping patients, while the Registry will define which patients are and which are not appropriate for either procedure. Evaluation of therapy would then be subject to formal decision analysis with meaningful data sets.[18] Two such trials sponsored by the National Heart, Lung, and Blood Institute are now underway: the Emory Angioplasty Surgery Trial and the Bypass Angioplasty Revascularization Investigation. Other trials are underway in Europe.

The implications of the choice of therapy are important from the standpoint of health care costs and reimbursement. In particular, older and sicker patients will have a higher complication rate after coronary surgery, and will also have a longer hospital stay.[19–21] Similar trends may also be noted for PTCA patients. In addition, there may be pressure to send patients to PTCA if it is perceived to be less expensive (whether true in the long run or not). While severity of illness has been shown to affect resource utilization,[22] the patterns of choice of major modalities of care and how they affect resource utilization are more complex, and relatively unexplored. Finally, as the population of patients with common but expensive procedures ages and becomes sicker, there may be reason to reevaluate prospective payment strategies.

Thus, the implications of this study are many, but the number of questions raised is greater. While patients with coronary artery disease at Emory University have gotten older and have more left ventricular dysfunction, the extent to which this may be generalized and to what types of institutions is unknown. National figures only confirm that the number of patients undergoing these procedures is increasing, especially among the elderly. While PTCA is becoming more common, its true value compared to other therapies remains unknown. Furthermore, how this population will change in the future can only be estimated. What is most clear is that the care of the patient with coronary disease is in a state of flux that may be anticipated to continue for some time to come.

Acknowledgment: We thank Dr. Robert Schlant and Dr. R. Wayne Alexander for careful review of the manuscript.

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Effects of Intravenous Isradipine on Left Ventricular Performance During Rapid Atrial Pacing in Coronary Artery Disease

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The effects of isradipine, a new dihydropyridine calcium antagonist, were evaluated in 24 patients referred for elective cardiac catheterization because of suspected coronary artery disease. Hemodynamics and left ventricular (LV) function (by digital subtraction angiography) were measured at baseline and during rapid atrial pacing (mean peak heart rate 135 beats/min), which induced chest pain or electrocardiographic changes in all patients. After a control pacing period, intravenous isradipine (0.01 mg/kg, n = 16) or placebo (n = 8) was administered in a double-blind fashion and all variables were measured again at baseline and during pacing to the same maximum heart rate. Before isradipine was given, pacing had no effect on systolic blood pressure, while increasing diastolic blood pressure (68 ± 8 to 87 ± 11 mm Hg, p <0.0001) and LV end-diastolic pressure measured in the immediate postpacing period (13 ± 5 to 18 ± 6 mm Hg, p <0.03) and decreasing LV end-diastolic volume index (59 ± 18 to 40 ± 12 ml/m², p <0.001), stroke volume index (37 ± 11 to 23 ± 10 ml/m², p <0.0001), ejection fraction (0.64 ± 0.07 to 0.53 ± 0.12, p <0.0003) and percent regional shortening in 4 of 5 myocardial wall segments. During pacing after isradipine, systolic and diastolic blood pressures were lower, ejection fraction was higher and percent regional shortening decreased in only 2 of 5 myocardial segments. In comparison to placebo, isradipine increased baseline heart rate, ejection fraction and stroke volume index while it decreased arterial pressure and end-systolic volume index before the second pacing period. These data demonstrate the effects of isradipine on LV performance both at rest and during rapid atrial pacing. Whether the effects on LV performance are totally explained by the lower afterload induced by isradipine or related to some other mechanism is not clear, but these findings do suggest that isradipine may be useful for the treatment of patients with exertional ischemia or hypertension.

(Am J Cardiol 1990;65:189–194)

Isradipine, an investigational dihydropyridine calcium antagonist, has been shown to have potent systemic and coronary vasodilating properties.[1,2] Clinical trials with oral isradipine suggest that it may be effective in the treatment of patients with systemic hypertension, angina pectoris and congestive heart failure.[3–5] However, differences exist among calcium antagonists with respect to their myocardial and electrophysiologic properties. In previous animal and human studies, isradipine had mild depressant effects on the sinus node without altering atrioventricular nodal conduction; thus it slightly attenuated the reflex tachycardia stimulated by the decrease in blood pressure.[1,6,7] Moreover, isradipine appears to have less cardiodepressant activity than other calcium antagonists.[2,6–8] These properties indicate that isradipine may be an effective agent for the treatment of myocardial ischemia. Therefore, we designed this study to investigate the acute effects of intravenous isradipine on left ventricular (LV) hemodynamics, volumes, ejection fraction and regional wall motion during rapid atrial pacing in patients with coronary artery disease (CAD).

METHODS

Patients: The study population consisted of 24 men referred for elective cardiac catheterization for the evaluation of CAD. All patients had chest pain and horizontal ST-segment depression of ≥1 mm during a standard treadmill exercise test. Patients with unstable angina, congestive heart failure, myocardial infarction within the last 3 months, known extensive LV wall motion abnormalities, LV end-diastolic pressure ≥25 mm Hg, important conduction system disease, bradycardia (<50 beats/min), uncontrolled hypertension or ST-segment abnormalities that would preclude the accurate interpretation of ischemic changes were excluded. Beta-adrenergic blocking drugs, calcium antagonists and long-acting nitrates were discontinued 24 hours before the study.

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Study protocol: A 6Fr pacing catheter was advanced from a femoral vein and positioned in the right atrium. A 7Fr micromanometer catheter (Millar Instruments) was advanced from a femoral artery and positioned in the left ventricle for pressure and dP/dt measurements. Aortic pressures were obtained with a fluid-filled catheter system connected to a transducer and referenced to atmosphere at the mid-chest level.

At baseline, a 12-lead electrocardiogram, aortic pressures, LV pressures, LV dP/dt and right anterior oblique digital subtraction left ventriculogram were obtained. Atrial pacing was then initiated at a rate 10 beats/min above the resting sinus rate and increased by 10 beats/min every 2 minutes until the onset of typical angina pectoris or ≥1 mm horizontal ST-segment depression was observed. The occurrence of angina or ST-segment depression was considered the endpoint of the pacing stress. Pacing was continued at this heart rate while a 12-lead electrocardiogram and all hemodynamic variables were measured. Atrial pacing was interrupted for a brief period (<30 seconds) during which LV end-diastolic pressure and a 12-lead electrocardiogram were again recorded. This was done to evaluate ST-segment changes in the absence of pacing artifacts and the response of the LV end-diastolic pressure immediately after pacing. After these were recorded, pacing was resumed at the previous rate for a minimum of 1 minute before another digital subtraction ventriculogram was performed. Pacing was terminated and a minimum of 10 minutes allowed for the hemodynamics to return to baseline. During pacing, up to 1 mg of atropine sulfate was administered if atrioventricular block occurred before the onset of chest pain or ST-segment changes.

After completion of the control pacing period, isradipine (0.01 mg/kg, n = 16) or placebo (n = 8) was administered by intravenous infusion in a double-blind fashion over 5 minutes. A placebo group was included to ensure that the observed changes in hemodynamics and wall motion during the second pacing period were an effect of isradipine and not related to repeated pacing and contrast administration. After completion of the infusion, a 12-lead electrocardiogram, all hemodynamic variables and a digital subtraction left ventriculogram were again recorded. Atrial pacing was repeated in a manner identical to that of the first pacing period. When the same maximal heart rate was achieved, all variables were measured in a fashion identical to the control pacing measurements. Coronary angiography was performed after completion of the study protocol. Significant CAD was defined as the presence of >50% luminal diameter narrowing in any major epicardial vessel as determined by visual analysis of the coronary arteriograms.

Digital subtraction methods and analysis: All left ventriculograms were acquired at end-inspiration in a 30° right anterior oblique projection using digital subtraction methods and nonionic contrast media (iohexol, 10 to 16 cc). All studies were acquired at 30 frames/s directly into a 512 × 512 image matrix of a dedicated computer system (ADAC Laboratories, 4100C). During pacing, left ventriculograms were recorded at the peak heart rate to optimize the detection of ejection fraction and wall motion changes.[9] An R-wave gated mask was derived from the cardiac cycle before the appearance of radiographic contrast and subtracted from the respective frames containing contrast. LV end-diastolic and end-systolic frames were selected visually and the outlines traced using a light pen. Premature and postpremature beats were not analyzed. LV volumes were calculated by the area-length method using a calibrated grid.[10] LV volumes and ejection fraction determined by digital subtraction angiography in our laboratory were compared with those derived by cineangiography in an independent group of 20 patients. LV volumes ($r = 0.92$, standard error of estimation = 14) and ejection fraction ($r = 0.91$, standard error of estimation = 0.03) correlated well with values obtained by cineangiography. Furthermore, intraobserver variabilities for digital volumes and ejection fractions were 7.8 and 8.7%, respectively and interobserver variabilities were 9.7 and 7.7%, respectively.

Regional wall motion analysis was performed using the center of mass method.[11,12] Briefly, a computer generated end-diastolic center of mass was derived and used as a reference point. One hundred cords were drawn from the center of mass to the end-diastolic and end-systolic endocardial borders and the percent shortening of each cord calculated. The average percent regional shortening for each of 5 segments (anterobasal, anterior, apical, inferior and inferobasal) was calculated.

Statistical methods: All values are expressed as the mean ± 1 standard deviation. Differences within the 2 treatment groups were evaluated by a repeated measures analysis of variance followed by a Newman-Keuls test. An unpaired *t* test was used to assess differences between treatment groups.

RESULTS

Patient population: There were no differences in age, incidence of previous infarction or number of coronary arteries narrowed between the placebo and isradipine groups. Furthermore, the baseline hemodynamic variables, LV volumes, ejection fraction and percent regional shortening were not different between the 2 groups (Tables I, II and III). During pacing before drug administration, 3 of 8 placebo- and 12 of 16 isradipine-treated patients developed ≥1 mm of horizontal ST-segment depression; angina-like chest pain occurred in 88 and 75% of the patients, respectively. After the respective drugs were given, there was an identical symptomatic and electrocardiographic response to pacing.

Effects of atrial pacing in patients receiving placebo: With the exception of LV end-diastolic pressure, which was slightly higher at baseline after placebo administration (16 ± 6 vs 13 ± 5 mm Hg, $p < 0.04$), there were no differences in the baseline or pacing variables after placebo administration (Table I). Furthermore, changes in LV volumes during pacing were similar before and after placebo administration (Table II). LV end-diastolic volume index and stroke volume index decreased while end-systolic volume index did not change

TABLE I Effects of Placebo or Isradipine on Left Ventricular Hemodynamics at Baseline and During Atrial Pacing

	Before Drug			After Drug		
	Baseline	Pacing	p Value	Baseline	Pacing	p Value
Heart rate (beats/min)						
Placebo	67 ± 15	135 ± 16	<0.0001	66 ± 12	134 ± 16	<0.0001
Isradipine	68 ± 11	135 ± 10	<0.0001	84 ± 11*†	134 ± 9	<0.0001
Systolic blood pressure (mm Hg)						
Placebo	141 ± 24	145 ± 33	NS	148 ± 21	143 ± 34	NS
Isradipine	139 ± 17	146 ± 22	NS	102 ± 13*†	117 ± 14*†	<0.0001
Diastolic blood pressure (mm Hg)						
Placebo	68 ± 7	89 ± 13	<0.002	73 ± 5	89 ± 12	<0.004
Isradipine	68 ± 8	87 ± 11	<0.0001	51 ± 5*†	68 ± 8*†	<0.0001
LV end-diastolic pressure (mm Hg)‡						
Placebo	13 ± 5	21 ± 6	<0.0004	16 ± 6*	20 ± 6	<0.02
Isradipine	13 ± 5	18 ± 6	<0.03	17 ± 5*	18 ± 7	NS
Positive dP/dt (mm Hg/s)						
Placebo	1,491 ± 193	2,188 ± 351	<0.0002	1,414 ± 191	1,973 ± 347	<0.0005
Isradipine	1,446 ± 271	2,127 ± 451	<0.0001	1,507 ± 274	2,214 ± 373	<0.0001
Negative dP/dt (mm Hg/s)						
Placebo	2,003 ± 342	2,188 ± 420	NS	1,918 ± 298	1,951 ± 419	NS
Isradipine	1,943 ± 360	2,071 ± 297	NS	1,500 ± 317*†	1,873 ± 349*	<0.0004

P values reflect the baseline to pacing comparisons within the respective groups; * p <0.05 vs the respective baseline or pacing value before drug; † p <0.05 vs the respective value in the placebo group; ‡ pacing measurement obtained immediately after the termination of pacing.
LV = left ventricular; NS = difference not significant.

TABLE II Effects of Placebo or Isradipine on Left Ventricular Volumes and Ejection Fraction at Baseline and During Atrial Pacing

	Before Drug			After Drug		
	Baseline	Pacing	p Value	Baseline	Pacing	p Value
End-diastolic volume index (ml/m^2)						
Placebo	52 ± 18	39 ± 13	<0.02	52 ± 16	37 ± 13	<0.0008
Isradipine	59 ± 18	40 ± 12	<0.001	62 ± 21	43 ± 12	<0.0001
End-systolic volume index (ml/m^2)						
Placebo	20 ± 11	19 ± 9	NS	19 ± 10	18 ± 10	NS
Isradipine	22 ± 10	19 ± 8	NS	17 ± 8	16 ± 6*	NS
Stroke volume index (ml/m^2)						
Placebo	32 ± 8	21 ± 5	<0.005	33 ± 7	19 ± 5	<0.002
Isradipine	37 ± 11	23 ± 10	<0.0001	44 ± 15*	28 ± 10†	<0.0001
LV ejection fraction						
Placebo	0.64 ± 0.10	0.57 ± 0.15	NS	0.65 ± 0.10	0.54 ± 0.13	<0.025
Isradipine	0.64 ± 0.07	0.53 ± 0.12	<0.0003	0.71 ± 0.09*	0.64 ± 0.10*†	<0.006

P values reflect the baseline to pacing comparisons within respective groups; * p <0.05 vs the respective baseline or pacing value before drug; † p <0.05 vs the respective value in the placebo group.
Abbreviations as in Table I.

TABLE III Effects of Placebo or Isradipine on Percent Regional Shortening at Baseline and During Atrial Pacing

	Before Drug (%)			After Drug (%)		
	Baseline	Pacing	p Value	Baseline	Pacing	p Value
Anterobasal						
Placebo	36 ± 10	29 ± 13	NS	34 ± 6	23 ± 10	<0.02
Isradipine	35 ± 8	27 ± 11	<0.01	40 ± 9	31 ± 15	<0.01
Anterolateral						
Placebo	33 ± 11	30 ± 14	NS	34 ± 10	28 ± 10	NS
Isradipine	33 ± 6	30 ± 10	NS	42 ± 9*	41 ± 10*†	NS
Apical						
Placebo	29 ± 7	26 ± 13	NS	30 ± 7	24 ± 10	NS
Isradipine	27 ± 6	21 ± 8	<0.005	32 ± 7*	29 ± 9	NS
Inferior						
Placebo	30 ± 14	25 ± 13	NS	29 ± 13	25 ± 12	NS
Isradipine	31 ± 9	25 ± 12	<0.01	37 ± 13*	30 ± 14*	<0.001
Inferobasal						
Placebo	25 ± 5	22 ± 7	NS	24 ± 5	18 ± 6	NS
Isradipine	22 ± 3	18 ± 6	<0.01	29 ± 7*	27 ± 8*†	NS

P values reflect the baseline to pacing comparisons within the respective groups; * p <0.05 vs the respective baseline or pacing value before drug; † p <0.05 vs the respective value in the placebo group.

during both pacing periods. Before placebo administration, the change in LV ejection fraction during pacing was not significant (0.64 ± 0.10 to 0.57 ± 0.15, difference not significant) whereas after placebo administration it was (0.65 ± 0.10 to 0.54 ± 0.13, $p < 0.025$).

The effects of pacing on percent regional shortening of the LV before and after placebo are listed in Table III. Before placebo administration, no segment demonstrated a significant decrease in percent regional shortening. During the pacing period after placebo, the anterobasal segment showed a significant decrease in regional shortening (34 ± 6 to 23 ± 10%, $p < 0.02$) while changes in the other regions were not different compared with the pacing period before placebo.

Effects of atrial pacing in patients receiving isradipine: Although a similar heart rate was achieved during pacing before and after isradipine, the baseline heart rate was greater after isradipine (Table I). Isradipine lowered systolic and diastolic blood pressure both at baseline and during pacing. Before isradipine, LV end-diastolic pressure increased in the immediate postpacing period (13 ± 5 to 18 ± 6 mm Hg, $p < 0.03$). After isradipine, baseline LV end-diastolic pressure was higher (17 ± 5 mm Hg, $p < 0.05$) and did not increase when pacing was terminated (18 ± 7 mm Hg). The effects of isradipine and pacing on peak positive and negative dP/dt are listed in Table I.

The effects of atrial pacing on LV volumes and ejection fractions are listed in Table II. LV end-diastolic volume index decreased in a similar fashion during pacing both before and after isradipine. There was no change in LV end-systolic volume index during pacing either before or after isradipine, but end-systolic volumes during pacing were smaller after isradipine. There was a decrease in stroke volume index during pacing both before and after isradipine administration; however, the baseline stroke volume index was greater after isradipine. LV ejection fraction decreased during pacing before (0.64 ± 0.07 to 0.53 ± 0.12, $p < 0.0003$) and after isradipine (0.71 ± 0.09 to 0.64 ± 0.10, $p < 0.006$), but after isradipine both the baseline and pacing values were greater than the respective values before the drug was given.

During the pacing period before isradipine, percent regional shortening declined significantly in 4 of the 5 segments (Table III). After isradipine was given, regional percent shortening declined by only 2 segments. At peak pacing, percent regional shortening was greater in the anterolateral, apical, inferior and inferobasal segments after isradipine.

Comparison of the effects of atrial pacing in the placebo and isradipine groups: Before either drug was given, similar changes in hemodynamics and LV volumes were detected during pacing among the placebo and isradipine groups with 1 exception (Tables I and II). In the placebo group, LV ejection fraction did not change during the initial pacing period. It decreased during pacing in the isradipine group. Changes in percent regional shortening before drug administration reflected the observed changes in ejection fraction; there were no changes during pacing in the placebo group while there was a decrease in 4 of the 5 segments in the isradipine group (Table III).

After drug administration, baseline heart rate was higher while systolic and diastolic blood pressures both at baseline and during pacing were lower in the isradipine group. Although LV end-diastolic pressure was higher at baseline after drug administration, there was no difference between the placebo and isradipine groups. Peak pacing LV stroke volume index and ejection fraction were higher in the isradipine-treated patients after drug administration compared with the placebo patients (Table II). Finally, compared with the placebo patients, percent regional shortening was higher in the anterolateral and inferobasal segments at peak pacing in those receiving isradipine (Table III).

DISCUSSION

Isradipine is a new dihydropyridine calcium antagonist that may be administered intravenously. Animal investigations have shown that isradipine has minimal negative inotropic effects on normal myocardium and potent effects as a vasodilator. It also inhibits sinus node function with little effect on atrioventricular conduction, a property that is rather unique among calcium antagonists.[2,6,7,13] In human studies, isradipine causes similar changes; peripheral vasodilation occurs as reflected by a decrease in systemic vascular resistance and increase in cardiac output.[1,8] The effects on heart rate are variable and seem to depend on the rate of administration and underlying cardiac diagnosis.[1,5,8] Isradipine also may have less negative inotropic effect compared with other calcium antagonists. Peak positive dP/dt and LV ejection fraction both increase when isradipine is given. However, because of the simultaneous changes in afterload and preload induced by isradipine, it is impossible to conclude that these changes represent a direct positive inotropic effect.[1,8] In contrast, when nifedipine is given alone, peak positive dP/dt does not increase despite an increase in heart rate and decrease in systemic vascular resistance indicating a negative inotropic effect of nifedipine.[8,14] Initial studies in patients with CAD suggest that oral isradipine decreases anginal frequency and ST depression during exercise treadmill testing.[4] These clinical findings are supported by the invasive findings in the present study that show that intravenous isradipine diminishes abnormalities of systolic performance that occur during atrial pacing in patients with CAD.

Alterations during ischemia induced by atrial pacing: Atrial pacing may not cause the same degree of myocardial ischemia as exercise stress testing at the same heart rate, but the alterations in hemodynamics and LV systolic performance caused by atrial pacing are well-described.[15–18] LV end-diastolic volume decreases during atrial pacing in patients with and without CAD. When atrial pacing causes myocardial ischemia, LV end-systolic volume does not change, ejection fraction decreases and new wall motion abnormalities are frequently detected.[16] Conversely, in the absence of pacing-induced ischemia, LV end-systolic volume decreases, ejection fraction either increases or is

unchanged and wall motion abnormalities are usually not observed.[19] Increases in LV end-diastolic pressure >5 mm Hg in the immediate postpacing period, transmyocardial lactate production and electrocardiographic changes all may occur during atrial pacing in patients with CAD, but are not invariable findings.[20] In our 2 patient groups, similar changes in hemodynamics occurred during the pacing periods before isradipine or placebo were administered. However, changes in several of the variables indicate that patients in the isradipine group may have been more prone to develop ischemia during atrial pacing despite an identical double product. During pacing, more patients in the isradipine group had electrocardiographic changes and there was a significant decrease in ejection fraction and percent regional shortening compared with the placebo group.

Effect of isradipine during atrial pacing: Isradipine caused several changes in LV performance both at baseline and during pacing. Consistent with its effects as a potent vasodilator, there was an increase in heart rate, stroke volume, ejection fraction and percent regional shortening as well as a decline in end-systolic volume and both systolic and diastolic blood pressure at baseline after isradipine. LV end-diastolic pressure was higher at baseline after isradipine, but also was higher in the placebo-treated patients. The presence of this finding in both groups indicates that it may have been related to the lingering effects of ischemia on diastolic function after the first pacing period or a mild residual depression of diastolic performance by the radiographic contrast agent.[21,22] Previous investigations have not consistently demonstrated a change in LV end-diastolic pressure after isradipine administration.[1,8] An alternative explanation for the increase in LV end-diastolic pressure after isradipine would be that the reflex tachycardia and vasodilation produced by isradipine increased oxygen demands and reduced coronary perfusion pressure distal to a critical stenosis thereby provoking myocardial ischemia. However, the increase in LV end-diastolic pressure in the placebo group after the control pacing period makes this explanation unlikely. A direct depressant effect of isradipine on LV diastolic function seems unlikely since other calcium antagonists of this type generally improve LV relaxation.[23,24] The lower peak negative dP/dt at baseline after isradipine in comparison with the placebo group may be a subtle manifestation of residual ischemia after the first pacing period since there is evidence that patients in the isradipine group were more prone to develop ischemia during the first pacing period.[25,26]

During the pacing period after isradipine, an identical heart rate was achieved, although both systolic and diastolic blood pressures were lower compared with the pacing period before drug. LV end-systolic volume was smaller with the same end-diastolic volume, thus ejection fraction was greater. Whereas regional percent shortening decreased significantly in 4 of 5 segments before isradipine, a significant decrease was observed in only 2 segments after isradipine. One possible explanation for the higher ejection fraction and improved regional shortening during pacing after isradipine is related to the lowering of the systolic pressure by isradipine. Since the double product was lower after isradipine, there may have been less ischemia produced, and thus LV ejection fraction and percent regional shortening were less impaired. With the methods used in this study, it is not possible to determine if isradipine had other favorable effects, such as improved coronary collateral flow, which may have partially alleviated the effects of ischemia on the left ventricle. Furthermore, the vasodilating effects of isradipine may have caused a reflex increase in LV contractility by enhancing sympathetic tone, thus partly masking the effects of ischemia and any direct negative inotropic effects of the drug. Although it was not possible to quantify the direct inotropic effects of isradipine in this study, a significant depressive effect on myocardial contractility seems unlikely.

Limitations: Although small volumes of nonionic contrast agents were used for the digital subtraction studies, the performance of multiple ventriculograms and lingering effects of myocardial ischemia from the first pacing period could adversely alter LV function during the second pacing period. Therefore, the inclusion of a placebo group in this study was especially important. With the exception of a persistently elevated LV end-diastolic pressure, all hemodynamic and functional measurements in the placebo group returned to their baseline value after the initial pacing period. Only 2 of the numerous variables measured—LV ejection fraction and percent regional shortening in the anterobasal segment—showed a worse response in the placebo group during the second pacing period. These observations support the conclusion that the changes noted in the isradipine group were related to the drug rather than the methods used.

Despite a lower double product after isradipine, the frequency of chest pain during pacing was not reduced. This may represent a limitation of atrial pacing as a form of stress rather than a lack of drug effect. Although some previous studies have suggested that chest pain during atrial pacing is a highly specific and sensitive marker of underlying CAD and ischemia, others[20] have shown that it is an unreliable indicator of ischemia occurring in 40% of patients without CAD or scintigraphic evidence of ischemia.

Clinical implications: The acute effects of intravenous isradipine demonstrated in this study suggest that it may be an effective agent for the treatment of patients with hypertension or exercise-induced myocardial ischemia. However, the response to long-term oral therapy will need further examination since it may differ from the acute hemodynamic effects demonstrated in this study. The demonstrated effects of isradipine as a vasodilator with limited negative inotropic properties suggest that it may be a beneficial drug in patients with depressed LV function. This is supported by initial studies in patients with congestive heart failure.[5] However, the effects of isradipine during rapid atrial pacing in this study were observed in a selected group of patients with normal LV ejection fractions. Whether similar effects will occur during periods of increased myocardial

oxygen demand in patients with depressed LV function must be determined.

Acknowledgment: We acknowledge the expert technical assistance of Barbara Hatfield, RN, Donald Haagen, RCPT, Janie McCoulskey, CCRN, Willie Gary and Graciela Fields during the performance of the hemodynamic studies.

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Value of a Revised Procainamide Test in the Wolff-Parkinson-White Syndrome

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A shortest preexcited RR interval <250 ms during atrial fibrillation identifies the patient with Wolff-Parkinson-White syndrome potentially at risk for ventricular fibrillation. Loss of preexcitation after infusion of up to 10 mg/kg of procainamide during sinus rhythm has been reported to correlate with a slow ventricular response during atrial fibrillation and has been proposed as a noninvasive test to establish risk of sudden death in these patients. Others have failed to establish this relation and have questioned the usefulness of the procainamide test. Such conflicting results were hypothesized to be a result of differing dosages and methodology. Consequently, this study tested the effect of incremental doses of procainamide (to a cumulative dose of 1 g) on the anterograde effective refractory period of the accessory pathway and related the reliability of the procainamide test to the dose at which preexcitation was lost. The effect of procainamide on the anterograde effective refractory period of the accessory pathway was dose dependent; patients who lost preexcitation had a steeper dose-response curve. Loss of preexcitation by a cumulative dose of 550 mg provided the best balance for sensitivity (60%) and specificity (89%) in identifying patients with preexcited shortest RR >250 ms. Specificity fell steeply after this dosage and higher doses were not useful. The diagnostic accuracy of the procainamide test is critically related to dosage and method of infusion.

(Am J Cardiol 1990;65:195–200)

Sudden death in the Wolff-Parkinson-White (WPW) syndrome is generally preceded by atrial fibrillation with a rapid ventricular response over the accessory pathway.[1–4] The risk of sudden death correlates best with shortest RR interval between 2 consecutive preexcited cycles in atrial fibrillation <250 ms, and attempts have been made to approximate this information noninvasively in patients with WPW.[5–7] Wellens et al[6] originally observed that intravenous procainamide (up to 10 mg/kg) infused during sinus rhythm blocked anterograde conduction over the accessory pathway when the effective refractory period was >270 ms. Noting a strong relation between effective refractory period and the ventricular rate during atrial fibrillation, Wellens and Durrer[8] extrapolated results to predict a long shortest RR and low risk of sudden death in the event of atrial fibrillation. Using higher procainamide dosages, Fananapazir et al[9] obtained different results and concluded that the procainamide test is nonspecific and unreliable. We hypothesized that such conflicting results were the result of differences in methodology and that the effect of procainamide is dose related. We evaluated the accuracy of predicting shortest RR >250 ms by loss of anterograde conduction over the accessory pathway after incremental doses of procainamide infused during sinus rhythm.

METHODS

Patients: Thirty-three consecutive patients referred for electrophysiologic study for symptomatic arrhythmias associated with the WPW syndrome were evaluated. Symptoms included palpitations, syncope and presyncope but no patient had documented ventricular fibrillation. There were 23 men and 10 women, aged 15 to 67 years (mean 32). No patient had associated cardiac disease as assessed by routine chest x-rays, echocardiogram and angiography when indicated.

Electrophysiology study: All patients underwent electrophysiology studies in the nonsedated, postabsorptive state after informed consent had been obtained. Antiarrhythmic agents were discontinued at least 5 half-lives before testing. The method of study for patients with preexcitation in our laboratory has been described.[10] Briefly, multipolar catheters were positioned in the coronary sinus, high right atrium, right ventricular apex and across the tricuspid valve for His bundle recording. Programmed atrial and ventricular stimulation was performed at 2 cycle lengths (generally 600 and 400 ms) at twice diastolic threshold with a rectangular pulse of 2 ms duration. Incremental atrial pacing was performed until atrioventricular block occurred and incremental ventricular pacing was performed to ven-

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triculoatrial block or to a cycle length of 250 ms. Accessory pathway location was determined by atrial mapping during reciprocating tachycardia in all patients and confirmed intraoperatively in 16 (48%) patients. As part of the study, atrial fibrillation was routinely induced by rapid atrial pacing (cycle length 50 to 200 ms) if it did not occur during the study.

Procainamide infusion: After control data were obtained, atrial fibrillation was induced and the shortest RR interval between 2 consecutive preexcited beats (shortest RR) was determined. After termination of atrial fibrillation, procainamide was infused incrementally with doses of 50, 100, 200, 400 and 250 mg every 10 minutes until a cumulative dose of 1 g or loss of preexcitation was achieved. The doses were given over 1 to 2 minutes in the supine position, except for the 400 mg dose, which was given over 3 to 4 minutes. Five surface electrocardiographic leads (I, II, III, V_1, V_6) were recorded continuously throughout. At the halfway point between doses, sinus cycle length and blood pressure were measured, a full 12-lead electrocardiogram was recorded and procainamide blood level was obtained. In addition, the anterograde effective refractory period of the accessory pathway was also determined at a cycle length 400 or 600 ms using steps identical to the control study. The same drive cycle length was used throughout an individual protocol. These measurements were all done with the patient in the supine position without manipulation of the intracardiac electrode catheters.

Statistical analysis: The Spearman rank test was used to determine the correlation between 2 variables, and the Student's *t* test was used to find significance between 2 groups. Analysis of the serial changes in effective refractory period after each dose of procainamide was done with analysis of variance for repeated measures, and the significance was determined by Tukey's test. Statistical significance was present when p was <0.05. All data are expressed as mean ± standard deviation.

RESULTS

The test was completed to a satisfactory endpoint in 28 patients. Five patients were excluded, 3 because of subtle preexcitation in sinus rhythm making subsequent assessment of preexcitation loss impossible. The fourth patient developed marked sinus bradycardia after a cumulative dose of 750 mg procainamide requiring atrial pacing for 10 minutes, and the fifth was excluded because of sustained atrial fibrillation that did not revert to sinus rhythm spontaneously. Otherwise there were no complications with no significant change in sinus cycle length (702 vs 683 ms) and a small decrease in mean arterial blood pressure (93 vs 87 mm, p = 0.001) af-

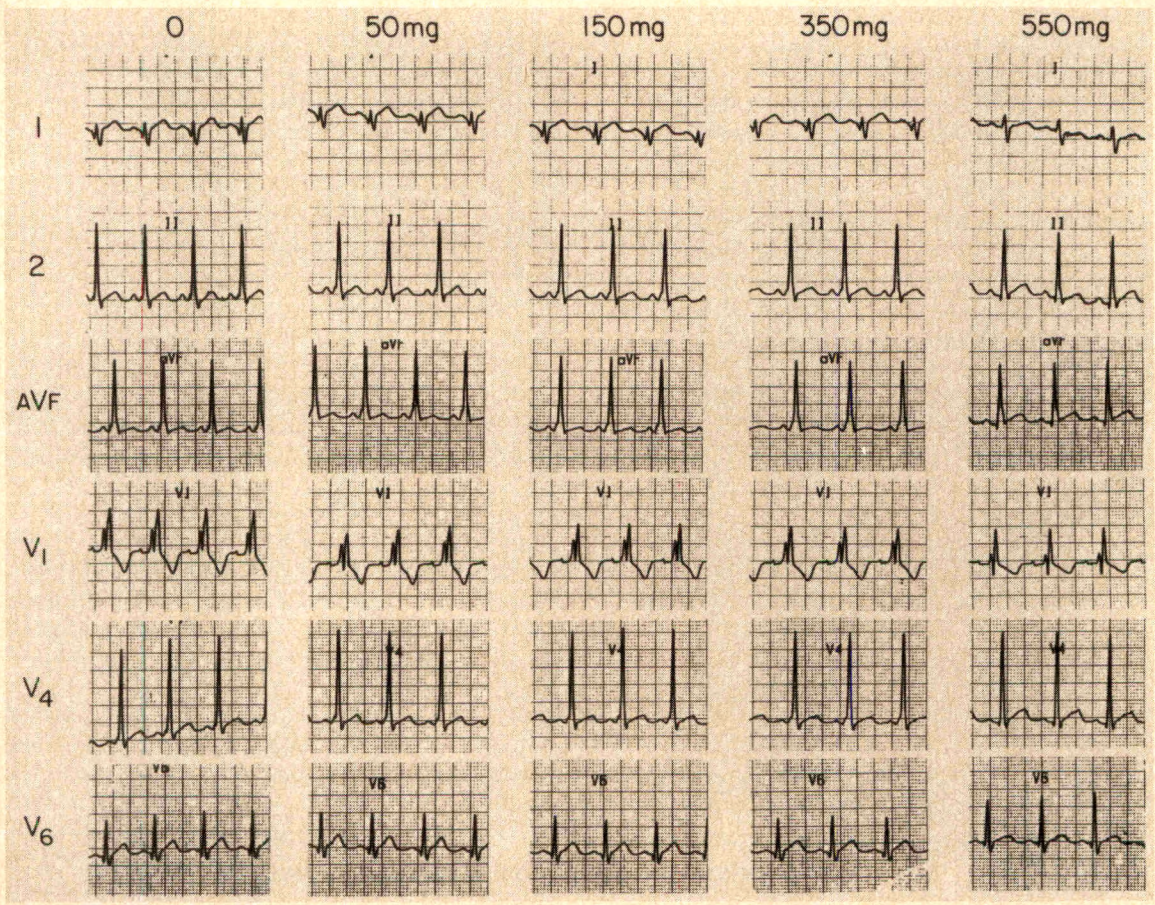


FIGURE 1. Effect of cumulative dose of procainamide on the preexcitation pattern. The delta wave is lost abruptly at a cumulative dose of 550 mg.

ter procainamide. Accessory pathways were distributed among all locations. There were 20 left parietal and 4 right parietal pathways. There were 2 anteroseptal and 9 posteroseptal pathways. Two patients had multiple pathways.

Effects of incremental doses of procainamide on the electrocardiogram: Patients generally lost preexcitation abruptly (Figure 1) or retained preexcitation. Occasionally, preexcitation became less evident but obviously did not disappear when seen in multiple leads. When preexcitation was subtle, gradual changes were not discernible even with multiple leads and determination of preexcitation loss was impossible (Figure 2).

Relation between effective refractory period and the shortest preexcited RR interval in atrial fibrillation: In agreement with previous studies,[4,8,9] we found a significant correlation between baseline effective refractory period and shortest RR during induced atrial fibrillation (Figure 3). However, the correlation was not strong ($r = 0.6$) and individual predictions of shortest RR from effective refractory period were not reliable. In 11 patients with shortest RR <250 ms, 5 (46%) had effective refractory period >270 ms. In 17 patients with shortest RR >250 ms, however, 15 (88%) had effective refractory period >270 ms.

Loss or persistence of preexcitation after procainamide: Nine patients had persistent preexcitation after a cumulative dose of 1 g of procainamide, while 19 patients lost preexcitation. Patients with persistent preexcitation had similar initial effective refractory periods compared to those retaining preexcitation (269 ± 45 vs 288 ± 36 ms, difference not significant), but shorter minimum RR during induced atrial fibrillation (224 ± 51 vs 300 ± 90 ms, $p = 0.03$). Those who retained preexcitation received higher doses of procainamide (1 g vs 513 ± 265 mg) and had higher serum levels of procainamide (47 ± 11 μm/liter vs 30 ± 17, $p = 0.001$) than those losing preexcitation. Although loss of preexcitation generally occurred with drug levels in the therapeutic range (17 to 42.5 μm/liter), this was not always the case. Thirty percent of patients requiring only low doses of procainamide (<550 mg) to abolish preexcitation had subtherapeutic drug serum levels.

Effect of incremental doses of procainamide on the effective refractory period: Effective refractory period increased after procainamide in all patients regardless of the initial effective refractory period. Furthermore, persistent preexcitation did not preclude statistically significant dose-related increases in effective refractory period. In the 9 patients with persistent preexcitation after 1 g of procainamide, mean effective refractory period increased from 269 ± 45 to 329 ± 99 ms ($p = 0.002$) (Figure 4). However, when analysis of variance was applied to the dose-response curve, there was an almost

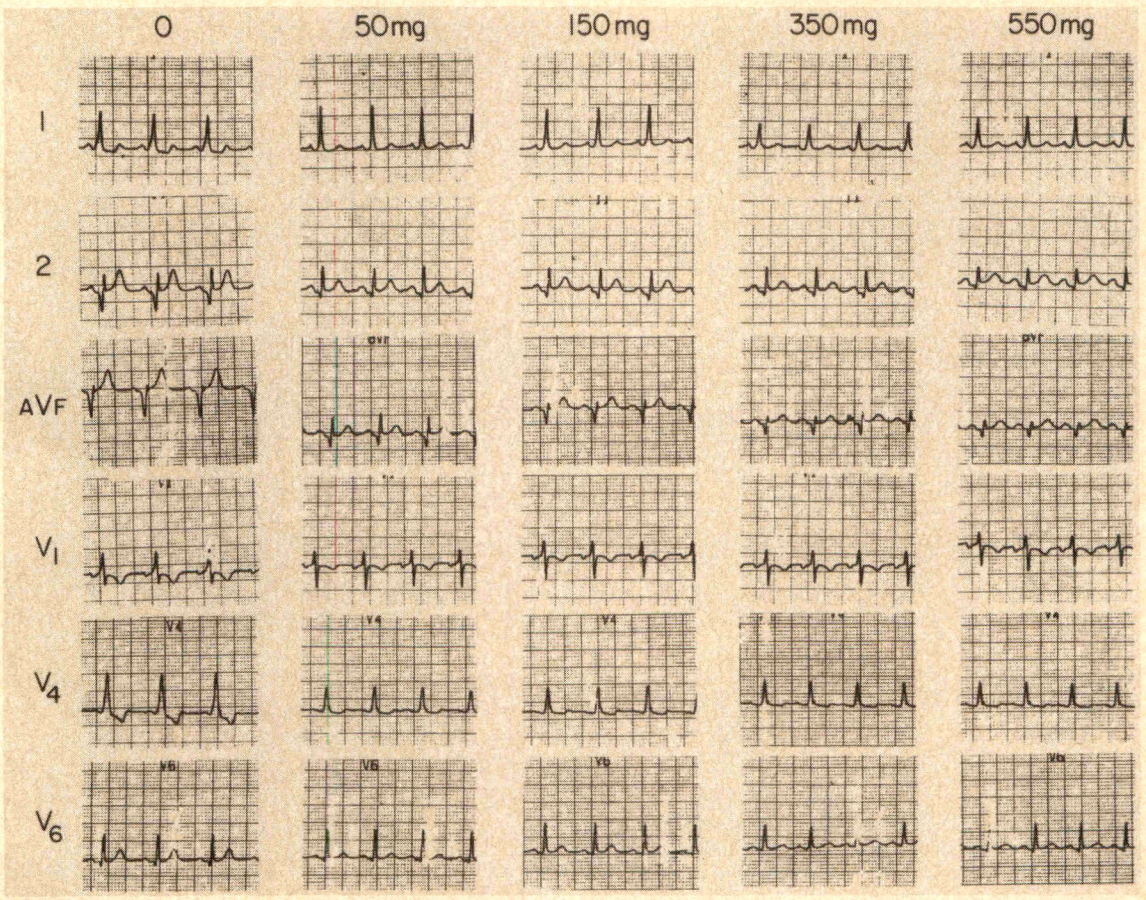


FIGURE 2. Gradual reduction in the preexcitation pattern with incremental doses. At a dose of 550 mg, it is still unclear whether preexcitation has been lost or fusion has merely shifted toward normal atrioventricular conduction.

TABLE I Comparison of Patients Losing Preexcitation with Doses up to 550 mg (Group A) to those Retaining Preexcitation (Group B)

	SRR (ms)	ERP (ms)	Dose of Procainamide (mg)	Serum Procainamide Concentration (μm/liter)
Group A (n = 13)	325 ± 98	294 ± 152	365 ± 152	22 ± 11
Group B (n = 15)	232 ± 45	271 ± 36	933 ± 114	47 ± 11
P value	0.003	NS	0.001	0.001

Data are mean ± standard deviation.
ERP = anterograde effective refractory period of the accessory pathway; NS = difference not significant; SRR = shortest preexcited RR interval during induced atrial fibrillation.

TABLE II Ability of Procainamide to Identify Shortest Preexcited RR Interval >250 ms by Normalization of QRS During Sinus Rhythm

Cumulative Dose (mg)	Sensitivity (%)	Specifity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
50	0	100	0	32
150	16	100	100	36
350	50	89	89	42
550	60	89	92	53
750	72	55	68	45
1000	74	40	74	44

True positive = loss of preexcitation with shortest RR >250 ms; true negative = persistence of preexcitation with shortest RR <250 ms; sensitivity = true positive/(true positive + false positive); specificity = true negative/(true negative + false positive); positive predictive value = true positive/(true positive + false positive); negative predictive value = true negative/(true negative + false negative).

imperceptible slope at low doses with statistical significance present only at a dose of 1 g ($p < 0.05$).

To gain further insight into the action of procainamide on the effective refractory period, we divided our patients into those who lost preexcitation at doses ≤550 mg (group A, n = 13) and those with persistent preexcitation after 550 mg (group B, n = 15) (Figure 5, Table I). We then analyzed each group by using analysis of variance for repeated measures and testing significance by Tukey's test. A dose of 550 mg was selected because it provided the optimum balance between sensitivity and specificity for the test (Table II).

Group A patients had a steep dose-response curve, with the increase in effective refractory period statistically significant by a cumulative dose of 150 mg procainamide ($p < 0.05$). Those in group B had a slower rate of change of effective refractory period with no statistically significant increase in effective refractory period until a cumulative dose of 750 mg. Since the initial effective refractory periods were similar in group A and B (294 vs 270, difference not significant), the steepness of the dose-response curve was the main differentiating factor between patients losing and retaining preexcita-

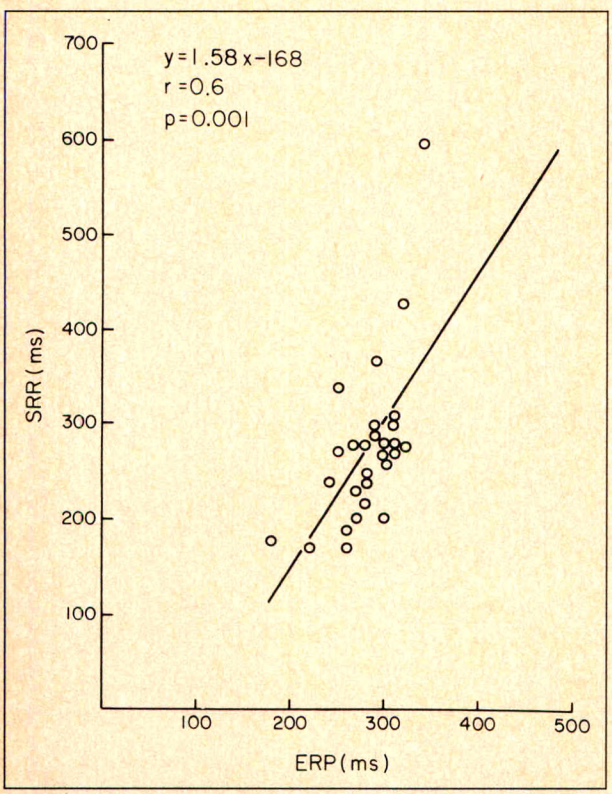


FIGURE 3. Correlation between shortest RR and effective refractory period in all patients studied. There is a direct correlation between shortest RR and baseline effective refractory period. ERP = anterograde effective refractory period of the accessory pathway; SRR = shortest RR interval between 2 preexcited beats during atrial fibrillation.

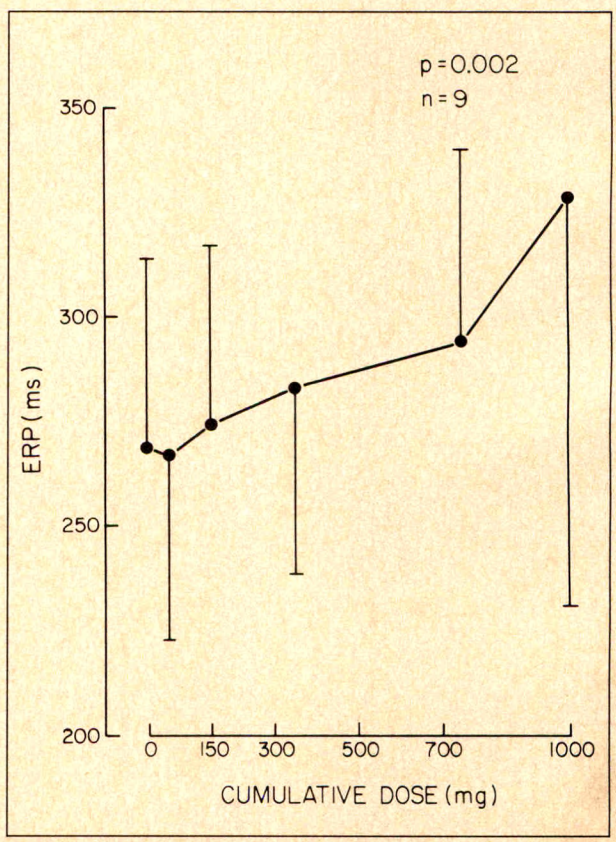


FIGURE 4. Change of effective refractory period after procainamide in 9 patients not losing preexcitation. There is a gradual increase in effective refractory period with dose but statistical significance is achieved only at a dose of 1,000 mg.

tion. Patients losing preexcitation with a dose <550 mg (group A) had longer shortest RR (325 ± 98 vs 232 ± 45 ms) (Table I) and had lower serum procainamide levels (22 ± 11 vs 47 ± 11 μm/liter) than those in group B (Table I). Patients with shorter shortest RR required higher a cumulative dose of procainamide to abolish preexcitation in sinus rhythm ($p = 0.03$, $n = 19$) (Figure 6).

The ability of the procainamide test to predict shortest RR >250 ms was dose dependent. Increasing procainamide dosage improves sensitivity at the expense of specificity (Table II).

DISCUSSION

Because the risk of sudden death in patients with the WPW syndrome is related to the development of very rapid heart rates during atrial fibrillation, a noninvasive test would help stratify patients according to ventricular response during atrial fibrillation. Wellens et al[6] observed that class 1 antiarrhythmic drugs had a relatively greater effect on accessory pathways with long versus short effective refractory periods. They observed that infusion of procainamide (up to 10 mg/kg) during sinus rhythm generally resulted in loss of preexcitation when the baseline effective refractory period was >270 ms and proposed this as a means of dividing patients with the WPW syndrome into high and low risk groups for developing sudden death. Fananapazir et al[9] subsequently reevaluated the procainamide test using different methodology and concluded that the effective refractory period was an unreliable predictor of minimum preexcited RR interval during atrial fibrillation and that the procainamide test was neither sensitive nor specific.

Our findings suggest that the differences in these studies are related to methodology. Our major observation is that the sensitivity and specificity of the procainamide test is critically related to the dose of procainamide with a good balance between sensitivity and specificity at a cumulative dose of <550 mg. The patient losing preexcitation at that dose tends to have a longer initial effective refractory period but is chiefly distinguished by having a steeper dose-response curve that relates dose to effective anterograde refractory period of the accessory pathway with procainamide. A very steep dose-response curve correlates with a slow ventricular response during atrial fibrillation and hence loss of preexcitation at a low dose is relatively specific in identifying the patient with a long shortest RR. However, failure to lose preexcitation at a low dose does not preclude the presence of a slow ventricular response and, conversely, loss of preexcitation at high doses can occur with any group.

In agreement with others, we found a significant correlation between shortest RR and effective refractory period.[4,8,9] Despite this, individual predictions of shortest RR from effective refractory period were frequently very misleading because of scatter and weak correlation. Sharma et al[11] observed that the deviations between shortest RR and effective refractory period

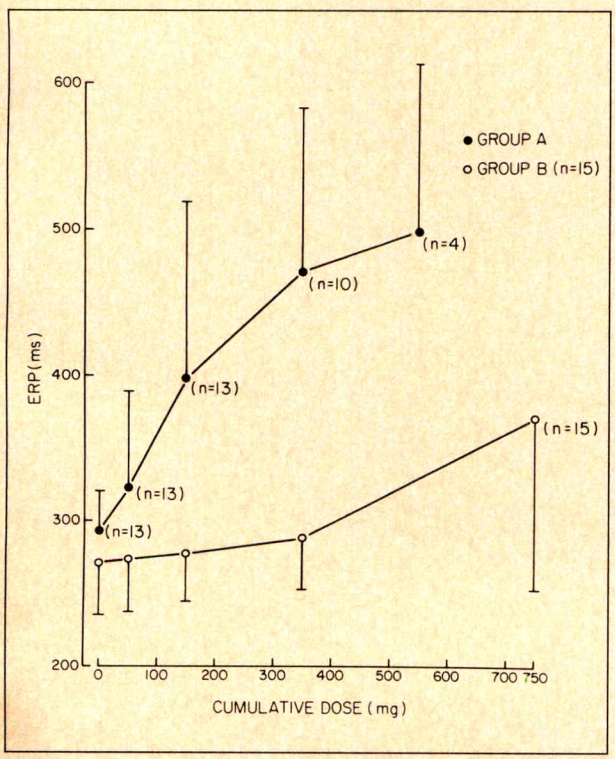


FIGURE 5. Rate of change of effective refractory period with cumulative doses of procainamide in group A (n = 13) and group B (n = 15). Group A = patients losing preexcitation by 550 mg of procainamide; group B = patients retaining preexcitation by same dose.

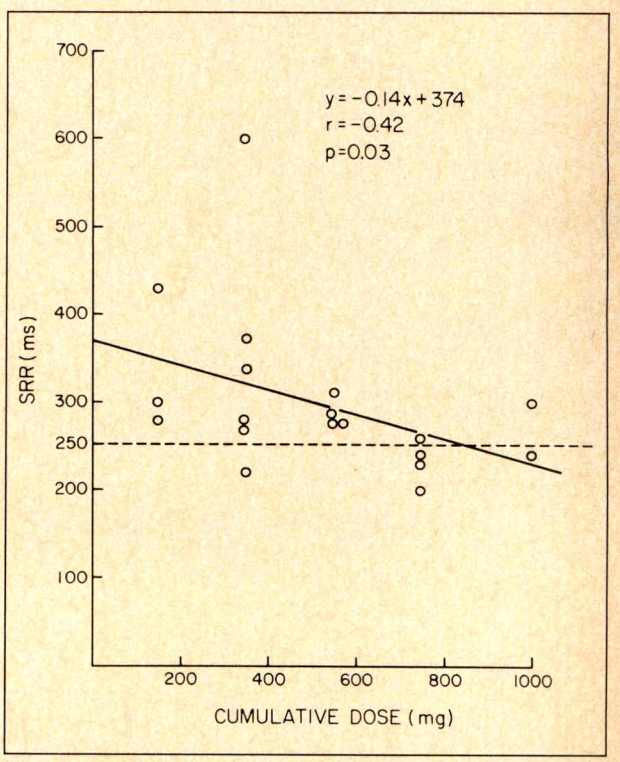


FIGURE 6. Correlation between shortest RR and cumulative dose of procainamide required to abolish preexcitation in sinus rhythm. Shortest RR = 250 ms, shown as the *dotted line*. Patients with shorter shortest RR initially require higher doses of procainamide to abolish preexcitation.

were dependent on the initial shortest RR. The shortest RR was overestimated by the effective refractory period when the shortest RR was short and underestimated when shortest RR was long.

Our data support the view that procainamide and probably other class 1 antiarrhythmic agents may be useful in identifying a patient with the WPW syndrome at low risk for ventricular fibrillation. Any such test will require a careful consideration of the dose-response relation between the drug and the effect on anterograde accessory pathway properties. The procainamide test has several limitations, which will probably be common to any pharmacologic test used for the same purpose. It will not be useful in patients in whom a relatively low dose of procainamide does not cause loss of preexcitation. Patients with minimal preexcitation on the surface electrocardiogram may be impossible to evaluate; abrupt loss of preexcitation with an antiarrhythmic drug is easier to judge in the patient with a greater degree of preexcitation. Finally, adverse reactions to procainamide including bradycardia and hypotension may occur. We, however, did not observe any at doses <550 mg, which, in fact, were the most useful dosages.

Acknowledgment: We wish to thank Sheila Doan and Susan Muir for preparation of the manuscript.

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Value of Programmed Ventricular Stimulation in the Evaluation and Management of Patients with Nonsustained Ventricular Tachycardia Associated with Coronary Artery Disease

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Programmed ventricular stimulation with up to 3 extrastimuli at the right ventricular apex was performed in 52 patients with spontaneous nonsustained ventricular tachycardia (VT) associated with coronary artery disease. There were 44 men and 8 women, aged 66 ± 9 years (range 45 to 86). The mean left ventricular ejection fraction was 41 ± 14%. Nonsustained VT was asymptomatic in 10 patients (19%), while the arrhythmia was detected during evaluation of palpitations in 5 patients (10%), presyncope in 11 (21%) and syncope in 26 patients (50%). All patients were tested in the drug-free state and were classified as having no inducible arrhythmia (31 patients, group I), or an inducible arrhythmia (21 patients, group II). The age, gender, type of heart disease, symptoms and left ventricular ejection fraction were similar in both groups. Group I patients had a higher overall incidence of syncope. Group I patients received no therapy, while group II patients received antiarrhythmic therapy guided by electropharmacologic testing. At 21 ± 17 months there was no sustained VT in either group. There were 3 deaths in group I patients, including 1 sudden, 1 nonsudden cardiac and 1 noncardiac death. In group II patients 6 deaths occurred including 4 nonsudden cardiac and 2 noncardiac deaths. In patients with nonsustained VT and coronary artery disease undergoing programmed ventricular stimulation, the incidence of significant arrhythmic events is low in those without therapy with no inducible arrhythmia, and in those with an inducible arrhythmia with therapy guided by electrophysiologic testing.

(Am J Cardiol 1990;65:201–205)

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Although the value of electrophysiologic testing in the evaluation and therapy of patients with sustained ventricular tachycardia (VT) or ventricular fibrillation has been established,[1–5] its role in predicting clinical outcome and selecting appropriate antiarrhythmic therapy in patients with nonsustained VT has not been adequately assessed.[6,7] The studies available report inconclusive and contradictory results in patients with nonsustained VT.[6–14] This prospective study was performed to examine the value of programmed ventricular stimulation in assessing the inducibility of ventricular arrhythmias, guiding therapy and predicting the clinical outcome in patients with spontaneous nonsustained VT.

METHODS

Patients: The study population comprised 52 consecutive patients with coronary artery disease referred to the Cardiac Arrhythmia Service of this institution for electrophysiologic evaluation of spontaneous nonsustained VT from August 1983 through March 1989. There were 44 men and 8 women, aged 66 ± 9 years (range 45 to 86). Thirty-one patients with noncoronary disease (n = 22) or no structural heart disease (n = 9) and clinical nonsustained VT who also had electrophysiologic studies during the same period were excluded from this study. The left ventricular ejection fraction, as measured with either contrast or radionuclide ventriculography or echocardiography in 46 patients, averaged 41 ± 14%. Nonsustained VT was asymptomatic and discovered in 10 (19%) patients during routine Holter monitoring performed late after infarction or for evaluation of premature ventricular beats found on routine electrocardiogram. The arrhythmia was detected during evaluation of palpitations in 5 patients (10%), presyncope in 11 (21%) and syncope in 26 patients (50%). In all patients nonsustained VT occurred in the absence of acute or recent (<1 month) myocardial infarction, antiarrhythmic therapy, long QT syndrome or electrolyte abnormalities.

Electrophysiologic study: The studies were performed in the nonsedated, postabsorptive state. All drugs with an antiarrhythmic effect had been discontinued for at least 5 half-lives before the study. Three quadripolar electrode catheters were introduced percutaneously through the femoral vein and were positioned

TABLE I Comparison of Clinical Variables in Groups I and II

	Group I	Group II	p Value
Sex: M/F	26/5	18/3	NS
Age (yrs)	68 ± 8	64 ± 9	NS
Symptoms (%)	25 (81)	17 (81)	NS
Syncope (%)	19 (61)	7 (33)	<0.05
Presyncope (%)	4 (13)	7 (33)	NS
Palpitations (%)	2 (6)	3 (14)	NS
LVEF (%)	42 ± 14	40 ± 14	NS
LVEF <35% (%)	8 (26)	6 (29)	NS
Follow-up (mos)	20 ± 17	23 ± 18	NS
Occurrence of SuVT	0	0	NS
Total cardiac deaths (%)	2 (6)	4 (19)	NS
sudden deaths (%)	1 (3)	0 (0)	NS

LVEF = left ventricular ejection fraction; SuVT = sustained ventricular tachyardia.

in the high right atrium, across the tricuspid valve (His bundle position) and the right ventricular apex under fluoroscopic guidance. Surface leads I, aVF and V_1 and intracardiac electrograms were simultaneously displayed on a multichannel recorder (Electronics for Medicine, VR-12). All data were stored on a magnetic tape for subsequent analysis and were retrieved on photographic paper at speeds of 50 to 200 mm/s. Programmed stimulation was performed with a constant current stimulator (Medtronic, model 5328) with rectangular pulses 2 ms in duration at 2 times diastolic threshold.

Incremental atrial pacing was performed at 100 beats/min or rates just above the sinus rate until atrioventricular block occurred. A single atrial extrastimulus was introduced in late diastole and moved earlier until atrial refractoriness was encountered at a pacing cycle length of 600 ms.[15] The ventricular stimulation protocol[16] consisted of single and double extrastimuli during sinus rhythm and after 3 basic drive cycle lengths of 600, 500 and 400 ms, and triple extrastimuli during sinus rhythm at the right ventricular apex. After the baseline study the patients with an inducible ventricular arrhythmia underwent serial electropharmacologic testing to find an effective antiarrhythmic therapy that prevented VT induction. The endpoints of stimulation were the induction of a sustained ventricular arrhythmia, reproducible nonsustained VT or completion of the protocol. During follow-up testing in patients with inducible sustained ventricular arrhythmia, programmed ventricular stimulation with up to triple extrastimuli after a pacing drive cycle length of 500 ms was performed.

Definitions: Clinical nonsustained VT, detected on telemetry, electrocardiography or Holter monitoring, was defined as at least 3 spontaneous consecutive beats

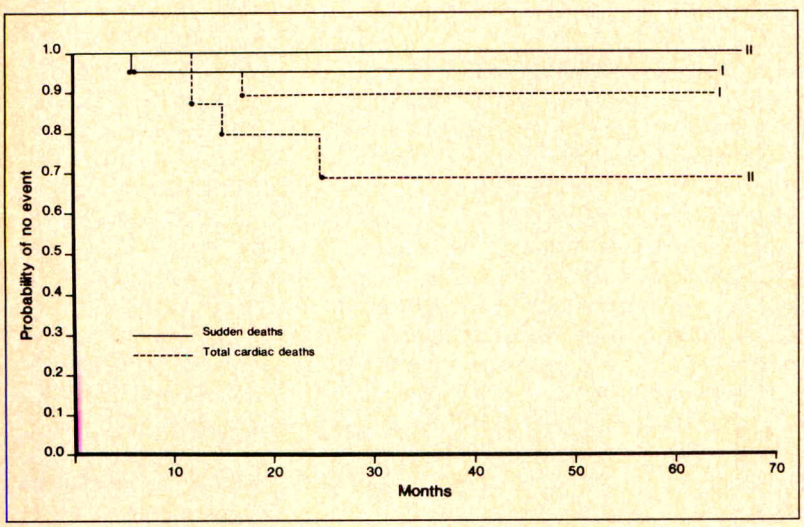


FIGURE 1. Life-table analysis with survival curves for sudden deaths and total cardiac deaths in patient groups I and II. No significant differences were noted between the 2 groups.

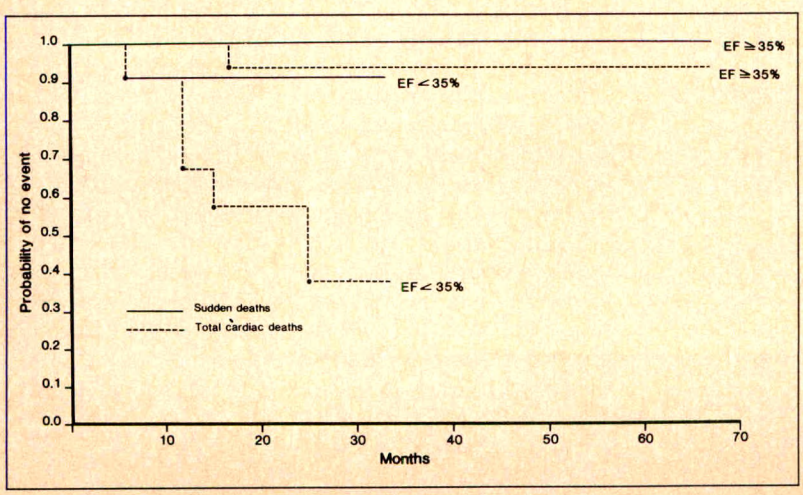


FIGURE 2. Life-table analysis with survival curves for sudden cardiac deaths and total cardiac deaths in patients with left ventricular ejection fraction (EF) of ≥35% and <35%. Significant difference in total cardiac death survival was noted between those with EF ≥35% (1 death) and those with EF <35% (5 deaths); p = 0.0010 by log-rank test or p = 0.013 by Wilcoxon test.

at a rate >100 beats/min and lasting <30 seconds in the absence of hemodynamic compromise. Induced nonsustained VT during electrophysiologic testing was defined as at least 6 beats of VT reproducibly induced and terminating spontaneously within 30 seconds. Sustained VT was defined as VT lasting >30 seconds or requiring termination due to hemodynamic compromise. VT was considered noninducible if <6 beats were induced with the completion of the stimulation protocol. Significant or major clinical arrhythmic event after hospital discharge included sudden death occurring within 1 hour of onset of symptoms or sustained ventricular arrhythmia with or without syncope or cardiac arrest.

Clinical follow-up: After hospital discharge the patients were followed up at the Cardiac Arrhythmia Clinic or by their referring cardiologists or by telephone contact every 3 to 6 months during the first year and every 6 to 12 months thereafter. Most recent contact was made by telephone in April 1989; the patient's current status and medications and history of any arrhythmic events were reviewed in detail.

Analysis of data: The data are presented as mean ± standard deviation. Statistical analysis was performed with 2-tailed *t* test for quantitative data and with chi-square test or Fisher's exact test for discrete variables. Survival probabilities were determined by the Kaplan-Meier method. Survival curves were compared with the log-rank and Wilcoxon tests. A p value <0.05 was considered significant.

RESULTS

Electrophysiologic study: At baseline drug-free electrophysiologic study, 31 patients (60%) had no inducible ventricular arrhythmia (group I) and 21 patients (40%) had an inducible arrhythmia (group II). Sustained VT was induced in 6 patients (12%), ventricular flutter or fibrillation in 5 patients (10%) and reproducible nonsustained VT in 10 patients (19%) (monomorphic in 5 and polymorphic in 5). In 14 patients the ventricular arrhythmia was induced with double extrastimuli (during ventricular pacing in 11 and during sinus rhythm in 3 patients), in 6 patients with triple extrastimuli and in 1 patient with atrial pacing. Among the 6 patients who required triple extrastimuli for arrhythmia induction, 2 had sustained VT induced, 3 had reproducible nonsustained VT (monomorphic in 1 and polymorphic in 2) and 1 had ventricular fibrillation induced. The cycle length of the induced VT (sustained or monomorphic nonsustained) was 247 ± 61 ms (range 200 to 420). A sustained arrhythmia was induced in 5 of 26 patients (19%) with syncope, 0 of 5 patients (0%) with palpitations, 2 of 11 patients (18%) with presyncope and 4 of 10 patients (40%) with no prior symptoms.

Electropharmacologic testing and antiarrhythmic therapy: All group II patients with inducible ventricular arrhythmia underwent electropharmacologic testing with 2.9 ± 1.4 antiarrhythmic drugs during repeat electrophysiologic studies in an attempt to find effective therapy to prevent arrhythmia induction. This was successfully accomplished in 16 patients, while 5 patients who had sustained VT induced at electrophysiologic study and failed conventional drug testing were finally given amiodarone. Ten patients were discharged receiving type Ia agents (5 quinidine, 1 procainamide, 2 disopyramide and 2 pirmenol), 2 receiving a combination of type Ia plus Ib (1 quinidine plus mexiletine and 1 procainamide plus mexiletine) and 1 receiving a type Ib agent (mexiletine) and 3 a type Ic agent (encainide). All group I patients were discharged without antiarrhythmic therapy.

Comparison of clinical variables in groups I and II: The age, gender, symptomatology and left ventricular ejection fraction are listed separately for the groups I and II in Table I. There were no significant differences between the 2 groups except for a higher prevalence of syncope in group I patients.

Long-term follow-up: During long-term follow-up 2 patients, 1 from each group, were lost to follow-up after 14 and 8 months, respectively. Over a mean follow-up of 21 ± 17 months, there was no documentation of spontaneous sustained VT but 9 deaths (17%) occurred. One (2%) was sudden, 5 (10%) were nonsudden cardiac (4 from heart failure and 1 from a myocardial infarction) and 3 (6%) were noncardiac (1 from small bowel infarction and 2 from cerebrovascular accidents). Among group I patients, followed for 20 ± 17 months, 1 patient (3%) died suddenly, 1 died of cardiac failure 2 days after coronary artery bypass surgery and 1 died of stroke. Among group II patients, followed for 23 ± 18 months, no sudden deaths occurred, but 4 nonsudden cardiac and 2 noncardiac deaths occurred. The left ventricular ejection fraction was lower (30 ± 16%) in the 6 patients who died from any cardiac causes compared with the ejection fraction of those who survived or died from noncardiac causes (43 ± 13%) ($p < 0.05$). Five of these 6 patients had an ejection fraction <35%. Survival curves with probability of freedom from sudden death and total cardiac death for groups I and II and those with ejection fraction ≥35% and <35% are shown separately in Figures 1 and 2. There were no differences between groups I and II, but a significant difference was noted in total cardiac death survival between those with ejection fraction ≥35% (1 death) and those with ejection fraction <35% (5 deaths) ($p = 0.0010$ by log-rank test or $p = 0.0013$ by Wilcoxon test).

Among group I patients 3 had recurrence of syncope over 1.5 to 3 years but with no documented arrhythmia. The diagnosis of vasovagal syncope was made in 1 patient and that of anxiety attacks with hyperventilation syndrome in another of these 3 patients. At 6 to 12 months after hospital discharge, 2 patients were started by their physicians on antiarrhythmic therapy with either quinidine or encainide for asymptomatic ventricular arrhythmias on Holter monitoring. One other patient was treated with flecainide for paroxysmal atrial fibrillation.

In 2 group II patients antiarrhythmic therapy had to be changed due to side effects from quinidine including fever, skin rash or elevation of liver enzymes. These 2 patients were switched to either procainamide or encainide and underwent repeat electrophysiologic testing. Finally, 1 group II patient discontinued his antiarrhythmic drug, mexiletine, after 2 years; he eventually died of progressive heart failure.

DISCUSSION

Spontaneous nonsustained VT serves as a marker of risk for sudden death in patients with acute myocardial infarction, dilated or hypertrophic cardiomyopathy or congestive heart failure,[17–22] while in other clinical settings it does not necessarily indicate the potential for development of sustained VT or sudden death.[12] Although the utility of electrophysiologic studies in patients with nonsustained VT needs to be defined,[6,7] stratification of risk for arrhythmic events by programmed ventricular stimulation is possible in such patients.[8–14,23] The sensitivity and specificity of programmed stimulation are lower in patients with nonsustained than sustained VT,[24,25] and vary according to the population studied and the stimulation protocol used.[8,9,11,12,26]

In the present study of a homogenous group with spontaneous nonsustained VT associated with coronary artery disease, a ventricular arrhythmia was induced in 21 of 52 patients (40%) (group II). These patients had clinical variables comparable with those of group I patients who had no inducible arrhythmia. Group II patients subsequently underwent serial electropharmacologic testing to determine effective antiarrhythmic therapy to suppress the inducible ventricular arrhythmia. This was achieved with conventional antiarrhythmic agents in 16 of 21 patients (76%) while 5 patients required amiodarone therapy. During long-term follow-up both groups had a low incidence of major arrhythmic events (0 to 3% incidence of sudden death). However, the total cardiac mortality was higher in patients with inducible ventricular arrhythmia (19% in group II vs 6% in group I) and those with left ventricular dysfunction (36% in patients with ejection fraction <35% vs 3% in patients with ejection fraction ≥35%).

Previous studies of patients with nonsustained VT have reported inducibility rates ranging from 34 to 69%.[10–13,23] Induction of sustained VT is reported in 0 to 21% of such patients. These rates are influenced by the presence and type of underlying structural heart disease and the degree of left ventricular dysfunction.[9] Few studies have reported on the long-term follow-up of these patients,[9,10,12–14,17,23] and in even fewer studies was antiarrhythmic treatment guided by the results of electrophysiologic testing.[9,12,14,17,23] Some of these studies showed a similar incidence of major clinical arrhythmic events in patients with and without inducible ventricular arrhythmias.[9,10,13] Other studies, however, have demonstrated that electrophysiologic testing can identify a low-risk subset of patients without inducible ventricular arrhythmias who have a favorable prognosis without antiarrhythmic therapy.[12,14,17,23] In 1 study of patients with an inducible arrhythmia, more sudden deaths (44%) occurred in the group receiving empiric therapy than in the group receiving therapy guided by electrophysiologic studies (7%).[14] An important clinical factor influencing cardiac mortality in these patients is the degree of left ventricular dysfunction. We confirmed this in the present study (Figure 2) but it is also shown in a number of previous reports.[9,13,17,19,23]

Our study confirms and further extends these observations by demonstrating a favorable prognosis not only for untreated patients without inducible arrhythmia (group I), but also for patients with an inducible arrhythmia (group II) who receive antiarrhythmic therapy guided by electrophysiologic testing. Failure of previous studies to demonstrate comparable results in patients with antiarrhythmic therapy guided by electrophysiologic testing may be due to differences in stimulation protocols, lower response rates to antiarrhythmic drug therapy,[12] difference in patient population,[17] or lack of adherence to recommended therapy.[19]

Acknowledgment: We acknowledge the skilled assistance of Melanie Marshall, RN, Keith Mack, RN, and Amy Payne, RN, with the electrophysiologic studies and patient follow-up, and the statistical expertise of Alexa Beiser, PhD, in the data analysis.

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Assessment of Hemodynamic Tolerance from a 24-Hour Intravenous Infusion of Fenoldopam Mesylate in Congestive Heart Failure

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To determine the maintenance of pharmacodynamic effects of fenoldopam mesylate, a dopamine-1 agonist, the invasive hemodynamic profiles of 33 patients with New York Heart Association functional class III to IV congestive heart failure were examined. Fenoldopam mesylate was initiated at 0.1 μg/kg/min and titrated to a cardiac index ≥25% above baseline. Upon achievement of optimal hemodynamics, maintenance infusion was begun (mean dose 0.6 μg/kg/min). Fenoldopam mesylate (baseline vs maximal effect) decreased systemic vascular resistance by 37% ($p < 0.001$), left ventricular filling pressure by 16% ($p < 0.05$) and mean arterial pressure by 11% ($p < 0.05$), with an associated augmentation in cardiac index and stroke volume index by 27% ($p < 0.001$). Attenuation of hemodynamic effect (maximal effect vs time) was noted in cardiac index (14% $p < 0.001$), systemic vascular resistance (13% $p < 0.05$) and stroke volume index (13% $p < 0.05$). None of the parameters exhibited complete attenuation to baseline values. Fenoldopam mesylate improves cardiac output and lowers systemic vascular resistance with relative attenuation of pharmacodynamic effect during a 24-hour intravenous infusion.

(Am J Cardiol 1990;65:206–210)

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Advancing cardiac failure leads to a diminishing cardiac output secondary to active vasoconstriction, increasing impedence to left ventricular outflow and limitation of vasodilation of both arteries and veins.[1] Neurohormonal activation of the sympathetic nervous system and renin-angiotensin system produces increasing levels of circulating norepinephrine and angiotensin, inducing vasoconstriction. Increased vascular sodium retention and interstitial pressure result in increased vasoconstriction. Therefore, the development of a compound that could attenuate these neurohormonal mechanisms, increase free water and sodium clearance and augment cardiac output would be beneficial in patients with congestive heart failure (CHF).

Fenoldopam mesylate (SK & F 82526J) is a synthetic postsynaptic dopaminergic receptor agonist,[2] possessing potent renal[2–4] and arteriolar vasodilating properties.[4,5] The renal vasodilatory dynamic alterations lead to increases in urine flow, fractional sodium excretion, creatinine and urea clearance and blunting of aldosterone release.[5,6] Augmentation of cardiac output, stroke volume and left ventricular ejection rate is associated with reduction in total peripheral resistance.[7,8] The agent has demonstrated, in intravenous and oral formulations, acute hemodynamic benefit (intravenous 6 hours, oral 4 hours) in New York Heart Association functional class II to IV CHF patients, while being relatively well tolerated.[7–9] Evidence of acute hemodynamic pharmacologic tolerance in CHF has been demonstrated in vasodilators.[10] Intravenous fenoldopam mesylate has exhibited sustained hemodynamic benefits for durations up to 6 hours. However, agents such as transdermal or intravenous nitroglycerin that maintain high serum concentrations for prolonged periods of time are associated with acute vascular tolerance.[11,12] This study was designed to evaluate the maintenance of beneficial pharmacodynamic effects of intravenous fenoldopam over infusion durations of 24 hours.

METHODS

Patient selection: The trial group consisted of 23 men and 10 women with CHF of at least 3 months' duration. The age range was from 29 to 87 years (mean ± standard error of the mean 65 ± 10). All 33 patients were classified as meeting the criteria for New York Heart Association functional class III or IV (signs and symptoms of peripheral or central congestion or both).

The mean radionuclide ejection fraction of the population was 21% (range 9 to 36). The cause of CHF was ischemic heart disease in 26 and idiopathic dilated congestive cardiomyopathy (normal coronary angiogram without obvious reason for left ventricular dysfunction) in 7 patients.

Written informed consent was obtained from each patient. The protocol was approved by each respective Institutional Review Board for Human Research.

The study was an open-label, 24-hour infusion of fenoldopam mesylate. Patients were excluded on the basis of pregnancy or lactation, primary obstructive valvular heart disease, obstructive cardiomyopathy, constrictive heart failure, primary pulmonary hypertension, myocardial infarction within 14 days before the study, cardiovascular event within the past 3 months or uncontrolled significant ventricular or supraventricular arrhythmias.

Hemodynamic measurements: After informed consent was obtained, right-sided heart catheterization was performed with a flow-directed, triple-lumen, balloon-tipped, thermodilution catheter positioned in the pulmonary artery in the standard fashion. The catheter was inserted 12 to 24 hours before the study day. The following hemodynamic parameters were measured (with the pressure transducer located at the level of the right atrium): mean right atrial pressure, pulmonary artery and left ventricular filling pressure, from hard copy printouts. All pulmonary artery pressures were measured at end-expiration. The post A wave, end-expiratory wedge pressure was monitored as the left ventricular filling pressure from hard copy printouts. Thermodilution cardiac outputs were done in triplicate using a cardiac output bedside computer (Edwards model 9520A), with a chart recorder, to evaluate thermyl curve integrity. Mean cardiac outputs varied by <10% (if the variance was >10%, 5 consecutive determinations were averaged). Systemic pressures were measured by mercury column or by radial artery cannulation and measured continuously using the SpaceLabs PCMS bedside monitor. Mean pressures were determined by electronic integration. The electrocardiogram was monitored continuously, and the heart rate was measured from the simultaneous electrocardiogram signal.

Derived hemodynamic variables were calculated as follows. Cardiac index (liters/min/m^2) = cardiac output (liters/min)/body surface area (m^2); stroke volume index (ml/m^2) = cardiac index/heart rate (beats/min); systemic vascular resistance (dynes · s · cm^{-5}) = 80 (mean systemic arterial pressure [mm Hg] − mean right arterial pressure [mm Hg])/cardiac output; pulmonary vascular resistance (dynes · s · cm^{-5}) = 80 (mean pulmonary artery pressure [mm Hg] − pulmonary capillary wedge pressure [mm Hg])/cardiac output.

Study chronology: The study was performed during a 3-day period in the cardiac care units of the respective institutions. On day 1 each patient underwent right-sided heart catheterization and SMA-20, complete blood count with differential, digoxin level, urinalysis, chest x-ray and 12-lead electrocardiogram were obtained. The patient was allowed to stabilize after withdrawal of his routine medications. Digoxin and diuretics were maintained at a constant level during the study period. Vasodilators including long-acting nitrates, angiotensin-converting enzyme inhibitors, calcium antagonists and β blockers were discontinued 12 hours before fenoldopam infusion. On day 2, baseline hemodynamic measurements were obtained every 30 minutes for 1.5 hours with the patient in the recumbent, fasting state. Food was allowed approximately 4 hours after drug infusion had begun, and the timing of meals and snacks was monitored throughout the infusion period. Patients were not permitted to eat until the goal hemodynamic variables had been obtained.

Drug administration was initiated at 0.1 μg/kg/min and titrated at maximum increments of 0.2 μg/kg/min every 20 minutes. Paired blood pressure and heart rates were recorded every 5, 10 and 20 minutes after each dose adjustment. Cardiac hemodynamics were measured every 20 minutes after a dose change. The goal of therapy was achievement of a cardiac output >25% above baseline. The development of significant tachycardia (>150 beats/min), hypotension (systolic blood pressure <70 mm Hg) or severe ventricular or atrial arrhythmias required reduction or termination of infusion dose.

After optimal dose determination, the fenoldopam infusion was maintained at a constant level for a period of up to 22 hours after infusion start. Hemodynamic measurements were monitored every hour for 10 hours, then every 2 hours thereafter (mean arterial pressure, heart rate), every 2 hours until 10 hours, and then every 4 hours (central venous pressure, pulmonary artery pressure, cardiac output). On day 3, the infusion was detitrated at 20% decrements every 20 minutes until terminated. Blood pressure and heart rate were monitored every 20 minutes and cardiac hemodynamics obtained every hour until the infusion was discontinued. The thermodilution catheter was then removed and patients were observed in-hospital for 24 hours.

Fenoldopam mesylate serum concentrations were measured at maximal effect (beginning of maintenance phase) and start of detitration phase, in a randomly selected subpopulation of 10 patients. For the purpose of comparison, they were treated in a similar way, and will be described separately.

Data analysis: All values are expressed as mean ± standard error of the mean. Statistical analysis involving comparisons of control data with individual time points was accomplished by the use of the *t* test for paired samples and the Bonferroni correction for multiple comparisons.[13] Statistical significance was accepted at a p value <0.05/K, where K = the number of comparisons performed.

RESULTS

Hemodynamic measurements: The infusion of fenoldopam mesylate (mean dose 0.6 μg/kg/min) increased cardiac index significantly from baseline (1.83 ± 0.37) to a maximal value of 2.52 ± 0.6 liters/min/m^2; this was a 27% increase (p <0.001) (Table I). A

TABLE I Hemodynamic Measurements of 24-Hour Infusion of Fenoldopam

Parameter	Baseline	Maximum	2 Hours	4 Hours	8 Hours	16 Hours	20 Hours	Detitration	Term
Cardiac index (liters/min/m^2)	1.83 ±0.3	2.52 ±0.6*	2.40 ±0.5*	2.32 ±0.6*	2.33 ±0.6*	2.16 ±0.6*	2.19 ±0.5*	2.04 ±0.5†	1.94 ±0.5
Heart rate (beats/min)	84 ±13	87 ±11†	87 ±11	87 ±11	86 ±10	84 ±10	84 ±10	83 ±10	83 ±10
LVFP (mm Hg)	25 ±8	21 ±8*	22 ±8†	22 ±9†	21 ±9†	24 ±9	21 ±7†	21 ±8†	24 ±8
Mean arterial pressure (mm Hg)	88 ±12	77 ±10*	79 ±12*	79 ±10*	79 ±9*	78 ±12*	80 ±10*	82 ±11*	85 ±13†
Mean PAP (mm Hg)	37 ±10	33 ±9†	34 ±10†	33 ±10†	33 ±11†	34 ±10†	33 ±8†	33 ±9†	37 ±9
PVR (dynes · s · cm^{-5})	312 ±128	227 ±88*	253 ±105*	238 ±90*	255 ±130†	217 ±106*	277 ±132	266 ±112†	318 ±120
RAP (mm Hg)	9 ±6	8 ±6	9 ±5	8 ±6	8 ±6	10 ±7	9 ±6	9 ±7	10 ±7
Stroke volume index (liters/beat/m^2)	22 ±6	30 ±9*	28 ±8*	28 ±8*	28 ±8*	26 ±9*	26 ±7*	25 ±8†	24 ±7
SVR (dynes · s · cm^{-5})	2,013 ±461	1,263 ±305*	1,383 ±351*	1,449 ±432*	1,498 ±479*	1,461 ±375*	1,555 ±468*	1,669 ±428*	1,756 ±476†

* $p < 0.001$; † $p < 0.05$ (baseline vs time).
LVFP = left ventricular filling pressure; PAP = pulmonary arterial pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure; SVR = systemic vascular resistance.

significant improvement in cardiac index from baseline was maintained throughout the measurement period of 24 hours. Concomitantly, stroke volume index increased from a baseline value of 22 ± 6 to a maximum of 30 ± 9 ml/m^2 ($p < 0.001$). The improvement in stroke volume index remained significant for the period of the infusion compared to baseline. Systemic vascular resistance declined progressively from a control value of 2,013 ± 461 to a nadir of 1,263 ± 305 dynes · s · cm^{-5} ($p < 0.001$). The significant decrease in systemic vascular resistance persisted throughout the observation period. Mean arterial pressure declined in concert with the systemic vascular resistance and exhibited a parallel statistical significant reduction from baseline. Heart rate did not change significantly during fenoldopam infusion. Accordingly, the increase in cardiac index is attributable to an increase in stroke volume. There was no rebound noted in systemic vascular resistance or mean arterial pressure with detitration or termination of the fenoldopam mesylate infusion.

The elevated baseline left ventricular filling pressure (25 ± 8) decreased to 21 ± 8 mm Hg ($p < 0.001$) at maximal effect and remained significantly reduced throughout the study period. Mean right arterial pressure exhibited no significant change during drug infusion.

Pulmonary artery pressure and pulmonary vascular resistance decreased in a significant fashion from 37 ± 10 and 312 ± 128 to 33 ± 9 mm Hg ($p < 0.05$) and 227 ± 88 dynes · s · cm^{-5} ($p < 0.001$), respectively. Significant reductions in these pulmonary parameters were maintained until termination.

Maintenance of hemodynamic effect: Attenuation of hemodynamic effect (maximum effect vs time) was initially noted at 2 hours (systemic vascular resistance), at 4 hours (cardiac index) and at 8 hours (stroke volume index) (Figure 1). The attenuation nadir over the measurement period occurred at 16 hours for cardiac index (2.52 ± 0.6 to 2.16 ± 0.6 liters/min/m^2, $p < 0.05$) and stroke volume index (30 ± 9 to 26 ± 9 ml/m^2, $p < 0.05$), and at 20 hours for systemic vascular resistance (1,263 ± 305 to 1,555 ± 468 dynes · s · cm^{-5}, $p < 0.05$). These effects were continuous until the infusion termination and were a universal finding across the study population. However, none of those parameters showed complete attenuation to baseline values. In contrast, heart rate, mean arterial pressure, right filling pressures and pulmonary pressures exhibited no attenuation of effect until infusion termination.

Pharmacodynamic subgroup: Fenoldopam mesylate serum concentrations were assayed in a randomly selected subset of 10 patients (Cleveland). The mean concentrations were 33 (maximal effect) and 32 ng/ml (20-hour maintenance phase), respectively. Hemodynamically, a lower cardiac index (1.60 ± 0.2 liters/min/m^2) and stroke volume index (18.8 ± 4 liters/m^2) were noted along with elevated filling pressures (left ventricular filling pressure 30 ± 9 mm Hg) (right atrial pressure 10 ± 5 mm Hg) in comparison to the entire population. Attenuation of hemodynamic effect was noted in cardiac index at 16 hours, stroke volume index at detitration and systemic vascular resistance at 16 hours. As noted in the entire population, no attenuation was seen in heart rate, mean arterial pressure, right filling pressures and pulmonary pressures among this subset. Additionally, no complete attenuation of effect was exhibited in this subgroup.

Clinical observations: Three patients required premature discontinuation of the infusion. Two patients exhibited increased biventricular filling pressures during dose escalation associated with sinus tachycardia in 1 patient; hypotension and decreased cardiac output occurred in both patients. In 1 patient reflex tachycardia did not occur perhaps secondary to advanced heart failure or concomitant amiodarone therapy blunting the chronotropic response to the arterial hypertension. A prolonged decrease in mean arterial pressure and concurrent symptomatic myocardial ischemia necessitated early termination in the third patient.

The most common adverse events were mild and transient. Headache (4 patients) and facial flushing (2 patients) were noted without requiring therapeutic in-

tervention or decrease in the infusion rate. Angina pectoris was observed in 2 patients with a history of stable angina during the dose-escalation phase and maintenance phase (14 hours), respectively. One patient required premature discontinuation of the infusion (14 hours). No cardiac arrhythmias or electrocardiographic evidence of myocardial ischemia were noted during the study. No hematologic or biochemical laboratory abnormalities were noted.

Overall, fenoldopam mesylate administration was associated with a 1 kg decrease in weight from 71.6 ± 15.5 to 70.6 ± 15.8 kg. Four patients gained more than 2.0 kg during the infusion accompanied by an increase in blood urea nitrogen in 3 and an exacerbation of peripheral edema in 2. The remainder of the population exhibited modest changes in weight.

DISCUSSION

This trial suggests that fenoldopam mesylate decreases systemic vascular resistance, left ventricular filling pressure and mean arterial pressure with an accompanying increase in cardiac index and stroke volume index. Initiation and termination of these dynamic changes are rapid, without demonstrable rebound effects. Furthermore, fenoldopam mesylate demonstrates a relative attenuation of pharmacodynamic effects over a 24-hour infusion.

Trials of fenoldopam mesylate (oral and intravenous) in patients with CHF have demonstrated similar hemodynamic profiles. Reductions in left ventricular filling pressures, systemic vascular resistance and mean arterial pressure have been associated with significant increases in cardiac output and stroke volume.[7–9] Fenoldopam has exhibited minimal changes in right-sided heart filling pressures, pulmonary artery pressures and heart rate.[7,8] These efforts were maintained over 4-(oral) and 6-(intravenous) hour time periods.

This is the first human trial demonstrating tachyphylaxis to intravenous fenoldopam in the setting of CHF. Tachyphylaxis is defined as an attenuation of effect despite stable pharmacologic serum levels.[14] Our results exhibit an attenuation of systemic vascular resistance, and an associated decline in cardiac index and stroke volume index from the ceiling effect (maximum cardiac output), in both the total and subset populations (stable serum concentrations). However, complete tachyphylaxis (hemodynamic effect return to baseline) was not seen, possibly secondary to premature discontinuation.

Attenuation of the hemodynamic effects of fenoldopam mesylate has been evaluated in animals and humans. Repeat intravenous bolus injections or a 15-minute intravenous infusion of fenoldopam in a hypertensive rat population exhibited a >30% tolerance from the attained maximum total peripheral resistance.[15] Oral fenoldopam mesylate administered for 3 consecutive days to 17 CHF patients revealed an increase in cardiac index, while decreasing mean arterial pressure, left ventricular filling pressures and systemic vascular resistance.[16] However, these effects returned to baseline within 3 hours and repeat dosing produced no prolongation of hemodynamic effect.[16] In comparison, our data show attenuation of cardiac index, stroke volume index, and systemic vascular resistance, without loss of effect on mean arterial pressure at 16 hours of the sustained infusion rate. Furthermore, serum concentrations of fenoldopam mesylate were maintained over the dosing interval in the subset of patients assayed. Therefore, attenuation of the hemodynamic effect of fenoldopam mesylate is not facilitated by increased metabolism or excretion over time.

A reduction in receptor affinity or number[13,14,17] and neurohormonal activation[10] has been associated with vasodilator tolerance in CHF. Dopamine-1 receptor blockade and activation of the neurohormonal forces (renin-angiotensin system) have also been postulated as dual mechanisms of tolerance development from fenoldopam mesylate. Recent evidence suggests that fenoldopam mesylate produces both agonist and functional antagonist properties at the dopamine-1 receptor.[14,18] Additionally, this dopamine-1 blockade may be time equivalent to the onset of the agonist activity of fenoldopam mesylate.[15] However, a reduction in the affinity or density of specific receptors mediating the action of fenoldopam mesylate may be a facilitating factor in the apparent receptor blockade.

Increased renin secretion has been demonstrated by fenoldopam mesylate in animal and human trials.[8,18,19]

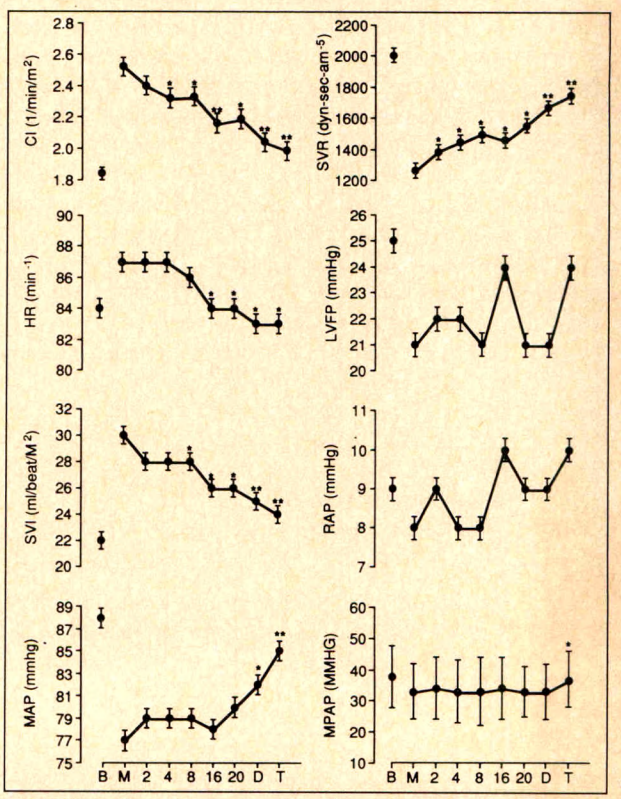


FIGURE 1. Hemodynamic values throughout the maintenance phase of fenoldopam infusion. Values are shown for cardiac index (CI), heart rate (HR), stroke volume index (SVI), mean arterial pressure (MAP), systemic vascular resistance (SVR), left ventricular filling pressure (LVFP), mean right arterial pressure (MRAP) and mean pulmonary artery pressure (MPAP), from maximum effect (M), through hour 2, 4, 8, 16, 20, detitration (D) and termination of infusion (T). B = baseline. Values are mean ± standard error of the mean. *p <0.05; **p <0.001.

Evidence suggests that the plasma renin elevation is secondary to stimulation of dopamine-1 receptors on the kidney juxtaglomerular cells.[19] Minimal increases in plasma norepinephrine and arginine vasopressin have also been documented while aldosterone secretion has not been suppressed with fenoldopam mesylate administration.[8] The increased renin secretion from fenoldopam mesylate stimulation may, therefore, increase angiotensin II levels, causing increased vasoconstriction and possibly attenuating the afterload reduction and enhanced renal function effects mediated by fenoldopam mesylate. In contrast, the expected rebound hemodynamic changes from activated neurohormonal forces, have not been noted upon fenoldopam mesylate withdrawal.[8] However, neurohormonal activation is uncommon in patients with severe left ventricular dysfunction (our study population).[20]

The renal effects of fenoldopam have been evaluated in the setting of hypertension[6,21,22] and CHF.[8] The agent increased renal plasma flow, urinary flow rate, glomerular filtration rate and sodium excretion in mild to moderate[6] and severe hypertensive[22] populations, respectively. However, in New York Heart Association functional class II to IV patients with CHF, no significant changes were demonstrated in urine volume, sodium or potassium excretion.[8] Although the renal blood flow index significantly decreased, in contrast to patients with hypertension,[8] our data, previously unreported, exhibited no significant change in serum creatinine and a nonsignificant decrease in blood urea nitrogen over the infusion period. The decrease in blood urea nitrogen may possibly be due to placing the study population at bedrest, withdrawal of diuretics, a direct effect of fenoldopam on enhancing renal blood flow or augmentation of cardiac output from fenoldopam.

In summary, the beneficial hemodynamic effects of fenoldopam were relatively attenuated through a 24-hour infusion in a patient population with severe CHF. Further evidence must be elucidated to clearly define whether complete attenuation occurs over longer infusion durations, the mechanism(s) facilitating attenuation of hemodynamic effect and lack of demonstrable renal effects of fenoldopam in patients with CHF. A clinical role for fenoldopam in CHF must be considered nonspecific at this time until further trials are completed.

Acknowledgment: We express our appreciation to E. Bednarczyk, PharmD, and Laura Cardello, BA, for their support.

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Hemodynamic and Renal Effects of Atrial Natriuretic Peptide in Congestive Heart Failure

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The hemodynamic and renal effects of anaritide (human atrial natriuretic peptide 102-126), a synthetic analog of atrial natriuretic peptide, were evaluated in 35 patients with chronic New York Heart Association class II to IV heart failure. There were 32 men and 3 women, aged 33 to 75 (mean ± standard error of the mean 56 ± 2) years. In the first phase of the study, right-sided heart catheterization was performed, and anaritide was administered as 1-hour infusions. The rate of the infusion varied among patients from 0.03 to 0.3 μg/kg/min. In response to anaritide, there were decreases in mean systemic arterial (94 ± 2 to 87 ± 2 mm Hg), right atrial (10 ± 1 to 8 ± 1 mm Hg), mean pulmonary arterial (33 ± 2 to 28 ± 2 mm Hg) and pulmonary artery wedge (22 ± 2 to 15 ± 2 mm Hg) pressures (all $p < 0.05$). Cardiac index increased (2.39 ± 0.15 to 2.62 ± 0.15 liters/min/m², $p < 0.05$) and heart rate was unchanged. Systemic vascular resistance decreased significantly, but pulmonary vascular resistance was unchanged. There were increases in urine volume (1.6 ± 0.2 to 2.3 ± 0.4 ml/min), sodium excretion (47 ± 13 to 74 ± 20 μEq/min) and fractional excretion of sodium (0.41 ± 0.11 to 0.59 ± 0.14%, all $p < 0.05$), while potassium excretion and creatinine clearance did not change.

In the second phase of the study, patients received 2-hour infusions of anaritide (0.03 to 0.6 μg/kg/min) and placebo with noninvasive monitoring. Mean systemic arterial pressure and plasma norepinephrine concentration decreased, while urine volume, sodium excretion and fractional excretion of sodium increased (all $p < 0.05$) during anaritide infusion, but were unchanged on placebo. Adverse effects, usually related to excessive reduction of systemic arterial pressure, were observed in 6 patients. Short-term infusion of atrial natriuretic peptide produces improvement in hemodynamics and renal function in patients with heart failure.

(Am J Cardiol 1990;65:211–215)

Atrial natriuretic peptide (ANP) has natriuretic, diuretic and vasodilator effects in healthy subjects.[1–5] Patients with heart failure have high levels of circulating immunoreactive ANP,[2,3,6–9] but may nevertheless have peripheral vasoconstriction and inadequate urine output. If this apparent lack of responsiveness to ANP can be overcome by administering pharmacologic doses of the hormone (or a synthetic analog), its diuretic and vasodilator properties may make it a useful agent for the management of patients with congestive heart failure. We therefore administered anaritide (human ANP 102-126) to patients with congestive heart failure, and measured its effects on hemodynamics and renal function.

METHODS

Patients: Thirty-five patients (32 men and 3 women), aged 33 to 75 (mean ± standard deviation 56 ± 2) years, were enrolled at 6 study sites. Eleven patients were in New York Association class II, 19 in class III and 5 in class IV. Some of the results for 6 patients at 1 site have been reported separately,[10] and results for 10 others are among those reported in another study.[11] Exclusion criteria were serum creatinine level >2.5 mg/dl or other evidence of renal disease, urinary tract abnormality that prevented complete bladder emptying or precluded placement of a bladder catheter, hepatic or endocrine disease, acute myocardial infarction within 3 months, standing systolic blood pressure <100 mm Hg or supine diastolic blood pressure >110 mm Hg, serum potassium level <3.5 mEq/liter, and hematocrit <30%. Women of childbearing potential were also excluded. The study was approved by the review boards of the participating institutions, and all patients gave written informed consent.

Study protocol: Beginning 2 days before the hospital admission, patients began a diet containing 20 mEq of sodium and 80 mEq of potassium daily, and all diuretic

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TABLE I Results of Initial One-Hour Infusions of Atrial Natriuretic Peptide

	All		0.03 μg/kg/min		0.1 μg/kg/min		0.3 μg/kg/min	
Parameter	Baseline	ANP	Baseline	ANP	Baseline	ANP	Baseline	ANP
HR	82 ± 2 (n = 35)	82 ± 3	78 ± 2 (n = 13)	77 ± 2	85 ± 5 (n = 13)	84 ± 6	81 ± 5 (n = 8)	85 ± 6
MAP	94 ± 2 (n = 35)	87 ± 2*	92 ± 4 (n = 13)	90 ± 4	96 ± 2 (n = 13)	86 ± 3*	95 ± 4 (n = 8)	82 ± 5
RAP	10 ± 1 (n = 33)	8 ± 1*	8 ± 1 (n = 13)	6 ± 1*	11 ± 2 (n = 13)	8 ± 2*	13 ± 4 (n = 6)	8 ± 3*
PAP	33 ± 2 (n = 35)	28 ± 2*	29 ± 3 (n = 13)	25 ± 4*	38 ± 3 (n = 13)	32 ± 4*	30 ± 5 (n = 8)	25 ± 5*
PCWP	22 ± 2 (n = 35)	15 ± 2*	18 ± 3 (n = 13)	14 ± 2*	26 ± 3 (n = 13)	17 ± 2*	20 ± 4 (n = 8)	11 ± 4*
CI	2.39 ± 0.15 (n = 34)	2.62 ± 0.15*	2.40 ± 0.14 (n = 13)	2.47 ± 0.17	2.20 ± 0.20 (n = 13)	2.46 ± 0.20*	2.86 ± 0.55 (n = 7)	3.29 ± 0.46
SVI	30 ± 2 (n = 34)	32 ± 2*	31 ± 2 (n = 13)	32 ± 2	27 ± 3 (n = 13)	30 ± 2	35 ± 6 (n = 7)	38 ± 5
SWI	30 ± 3 (n = 34)	32 ± 2	31 ± 3 (n = 13)	33 ± 3	27 ± 4 (n = 13)	29 ± 3	38 ± 8 (n = 7)	37 ± 5
SVR	1,642 ± 87 (n = 32)	1,417 ± 84*	1,534 ± 123 (n = 13)	1,505 ± 136	1,750 ± 147 (n = 13)	1,392 ± 114*	1,594 ± 256 (n = 5)	1,151 ± 258
PVR	227 ± 26 (n = 34)	233 ± 28	185 ± 29 (n = 13)	185 ± 31	276 ± 48 (n = 13)	273 ± 49	195 ± 68 (n = 7)	217 ± 84
UV	1.6 ± 0.2 (n = 33)	2.3 ± 0.4*	1.4 ± 0.2 (n = 13)	1.9 ± 0.5	1.6 ± 0.5 (n = 12)	2.9 ± 0.7*	2.0 ± 0.6 (n = 7)	2.2 ± 0.9
UNa	47 ± 13 (n = 31)	74 ± 20*	44 ± 20 (n = 12)	58 ± 29	32 ± 17 (n = 12)	72 ± 30*	88 ± 38 (n = 6)	120 ± 64
UK	67 ± 7 (n = 31)	70 ± 6	78 ± 14 (n = 12)	67 ± 10	54 ± 8 (n = 12)	78 ± 11	63 ± 8 (n = 6)	63 ± 10
Ccre	100 ± 11 (n = 29)	93 ± 8	120 ± 25 (n = 10)	107 ± 11	77 ± 11 (n = 11)	83 ± 10	109 ± 19 (n = 7)	91 ± 24
FENa	0.41 ± 0.11 (n = 29)	0.59 ± 0.14*	0.31 ± 0.12 (n = 10)	0.49 ± 0.17*	0.27 ± 0.11 (n = 11)	0.53 ± 0.20	0.79 ± 0.38 (n = 7)	0.90 ± 0.43

* $p < 0.05$ vs baseline.
Values are mean ± standard error of the mean.
ANP = atrial natriuretic peptide; Ccre = creatinine clearance (ml/min); CI = cardiac index (liters/min/m^2); FENa = fractional excretion of sodium (%); HR = heart rate (beats/min); MAP = mean systemic arterial pressure (mm Hg); PAP = mean pulmonary arterial pressure (mm Hg); PCWP = pulmonary capillary wedge pressure (mm Hg); PVR = pulmonary vascular resistance (dynes s cm^{-5}); RAP = right atrial pressure (mm Hg); SVI = stroke volume index (ml/m^2); SVR = systemic vascular resistance (dynes s cm^{-5}); SWI = stroke work index (g-m/m^2); UK = urinary potassium excretion (μEq/min); UNa = urinary sodium excretion (μEq/min); UV = urine volume (ml/min).

and vasodilator medications were withheld. Substances known to affect sodium balance, including caffeine, steroids and nonsteroidal antiinflammatory drugs, were also withheld. Other medications, including digoxin, were continued.

On the second hospital day, digoxin was withheld, and patients had a light breakfast of juice, gelatin and a decaffeinated beverage. A bladder catheter, a radial artery cannula and a balloon-tipped flow-directed pulmonary artery catheter were inserted. After confirmation of baseline hemodynamic stability (variation between repeat measurements <10%), three 1-hour infusions of anaritide were administered in ascending dose order, separated by 1-hour recovery periods. Patients received one of the following dose sequences: 0.03, 0.06 and 0.1 μg/kg/min, 0.1, 0.2 and 0.3 μg/kg/min or 0.3, 0.45 and 0.6 μg/kg/min. Initial infusion rate was 0.03 μg/kg/min in 13 patients, 0.06 μg/kg/min (due to a technical error) in 1, 0.1 μg/kg/min in 13 and 0.3 μg/kg/min in 8. Persistent carry-over effects of the 1-hour day 2 infusions were present after the 1-hour "recovery" periods, and would therefore affect the "baseline" measurements for subsequent infusions. At the end of first 1-hour recovery period, mean systemic arterial pressure was 7%, right atrial pressure 14% and pulmonary artery wedge pressure 21% lower than values before the first 1-hour infusion (all $p < 0.01$), while cardiac index was unchanged. For this reason, the effects of only the initial 1-hour infusion in each patient were analyzed.

The volume of urine excreted during each hour was replaced during the subsequent hour with an infusion of 5% dextrose in 0.3 normal saline. Urine volume, heart rate, systemic arterial, right atrial, pulmonary arterial and pulmonary artery wedge pressures, thermodilution cardiac output, serum and urine sodium, potassium and creatinine levels were measured before and during each infusion. The bladder, pulmonary artery and radial artery catheters were removed at the end of the study period on day 2.

On days 3 and 4, patients received, in random order, a 2-hour infusion of anaritide at the highest dosage administered on day 2 without side effects, and a 2-hour infusion of placebo (consisting of mannitol-acetic acid vehicle). Three patients dropped out of the study after day 2: 1 experienced vomiting during anaritide infusion on day 2; 1 had angina following the day 2 study; and 1 had preexisting but previously unrecognized anemia in the setting of a pulmonary malignancy. Infusion rate was 0.03 μg/kg/min in 1 patient, 0.06 μg/kg/min in 4, 0.1 μg/kg/min in 10, 0.3 μg/kg/min in 11, 0.45 μg/kg/min in 1 and 0.6 μg/kg/min in 5. Heart rate and blood pressure were measured and urine samples were collect-

ed during a baseline period and during the infusion of anaritide or placebo. Plasma immunoreactive ANP concentration was measured before the start of the infusions, and at the end of the 2-hour infusion. Plasma renin activity and aldosterone and norepinephrine concentrations were measured before and at the end of anaritide infusion.

Data analysis: Some data were not collected for all patients in the study, and some were missing because of technical inadequacies in their collection. Cardiac index, stroke volume index, systemic and pulmonary vascular resistance, creatinine clearance and fractional excretion of sodium were calculated from standard formulas. Mean systemic arterial pressure was calculated as [(systolic pressure) + 2 (diastolic pressure)]/3. Stroke work index (g-m/m^2) was calculated as 0.0136 × stroke volume index × (mean systemic arterial pressure − pulmonary artery wedge pressure). Plasma ANP and aldosterone concentrations and renin activity were determined by radioimmunoassay, as previously described.[11,12]

Statistical methods: Values are expressed as mean ± standard error of the mean. Comparisons between 2 treatment periods (e.g., baseline and anaritide for the 1-hour infusion) were made by paired *t* tests. Overall comparisons among 4 treatment periods (baseline, placebo, baseline and anaritide for the 2-hour infusion) were made by 2-way analysis of variance; comparisons of group means were made using Neuman-Keuls test. Differences were considered significant if the p value was <0.05.

RESULTS

Baseline characteristics: On the day of the 1-hour infusions, baseline right atrial, mean pulmonary arterial and pulmonary artery wedge pressures were elevated above normal values, and cardiac index was depressed (Tables I and II). Creatine clearance was normal; values for the 1-hour infusion, placebo and 2-hour infusion days were similar. On the day of the 2-hour anaritide infusion, baseline plasma renin activity and aldosterone and norepinephrine concentrations were elevated above normal values in the subsets of patients in whom these measurements were made. Baseline plasma ANP concentrations were elevated at 94 ± 26 (n = 24) on day 2, 70 ± 10 (n = 24) on the day of placebo infusion and 73 ± 9 ng/dl (n = 26) on the day of the 2-hour anaritide infusion.

Hemodynamic effects of one- and two-hour infusions: In response to the 1-hour infusion of anaritide, mean systemic arterial, right atrial, mean pulmonary arterial and pulmonary artery wedge pressures decreased significantly (Table I, Figure 1). Heart rate did not change. Cardiac index increased from 2.39 ± 0.15 to 2.62 ± 0.15 liters/min/m^2 ($p < 0.01$). Stroke volume index increased by a small but statistically significant amount, but stroke work index did not change. Systemic vascular resistance decreased, but pulmonary vascular resistance did not change.

At the end of the 2-hour infusion of anaritide, plasma ANP concentration was 6,790 ± 834 ng/dl (n = 24). Mean arterial pressure decreased with anaritide, and was not affected by placebo infusion (Table II, Figure 2). Heart rate did not change during infusion of either anaritide or placebo.

Renal effects of one- and two-hour infusions: Urine output, sodium excretion and fractional excretion of sodium increased during the 1- and 2-hour infusions of anaritide, and were unchanged during placebo infusion (Figures 1 and 2, Table I). Urinary potassium excretion and creatinine clearance did not change with anaritide.

Endocrine effects of two-hour infusions (Table II): Plasma concentration of norepinephrine decreased during the 2-hour anaritide infusion. Plasma renin activity and aldosterone concentration did not change.

Adverse effects of infusions: Six patients had significant adverse effects during or after anaritide infusion. One had hypotension (blood pressure 80/60 mm Hg) at the end of a 1-hour infusion of anaritide, 0.45 μg/kg/min; after a 2-hour infusion of anaritide, 0.3 μg/kg/min, he had syncope after standing to void, with blood pressure 80/50 mm Hg immediately afterward. A second patient had orthostatic hypotension (systolic blood pressure 48 mm Hg) 1 hour after a 1-hour infusion of anaritide, 0.1 μg/kg/min. Another patient had hypotension (blood pressure 82/54 mm Hg) at the end of a 1-hour infusion of anaritide, 0.45 μg/min. A fourth patient had anuria during a 1-hour infusion of anaritide, 0.1 μg/kg/min, but subsequently had a 2-hour infusion at the same dosage without adverse effect. A fifth patient vomited during a 1-hour infusion of anaritide, 0.3 μg/kg/min. These adverse effects were managed with discontinuation of the infusion or administration of fluids. The final patient experienced angina after the final infusion of a 0.03, 0.06 and 0.1 μg/kg/min sequence; this patient had had chronic stable angina. There were no adverse effects of placebo infusion.

DISCUSSION

Hemodynamic effects of atrial natriuretic peptide: We have demonstrated an improvement in hemodynamics, characterized by a decrease in filling pressure and an increase in cardiac output, in patients with heart failure in response to infusion of anaritide. This finding confirms the results of 3 previous studies in smaller numbers of patients.[3,5,13] The effects of ANP on stroke volume and cardiac output in heart failure are in contrast to those seen in the presence of normal left ventricular systolic function. In normal animals, cardiac output decreases during ANP infusion.[14–16] Cody et al[3] observed no change in cardiac output in response to ANP in normal humans. Patients with hypertension exhibit a decrease in cardiac output in response to ANP.[17] While part or all of these effects may be accounted for by a decrease in preload, the possibility that ANP depresses myocardial contractility has been raised.[17] The increase in cardiac output observed in patients with heart failure is likely explained by the higher initial preload, a more horizontal ventricular function curve, a predominantly vasoconstrictor neurohormonal profile and a greater sensitivity to afterload reduction in these patients. A preliminary report of an investigation of the direct myo-

TABLE II Results of Two-Hour Infusions of Placebo and Atrial Natriuretic Peptide

	All				0.1 μg/kg/min				0.3 μg/kg/min			
	Placebo		ANP		Placebo		ANP		Placebo		ANP	
Parameter	Baseline	Infusion	Baseline	Infusion	Baseline	Infusion	Baseline	Infusion	Baseline	Infusion	Baseline	Infusion
HR	80 ± 2 (n = 32)	78 ± 2	80 ± 2	77 ± 2	76 ± 3 (n = 10)	74 ± 3	78 ± 4	74 ± 3	82 ± 4 (n = 11)	79 ± 3	79 ± 3	77 ± 2
MAP	92 ± 2 (n = 32)	93 ± 2	93 ± 2	84 ± 2*†	85 ± 4 (n = 10)	91 ± 4*	89 ± 4	81 ± 5*†	96 ± 5 (n = 11)	95 ± 4	95 ± 4	85 ± 4*†
UV	2.1 ± 0.4 (n = 19)	1.7 ± 0.3	1.9 ± 0.3	3.0 ± 0.4*†	1.9 ± 0.5 (n = 6)	1.6 ± 0.4	1.9 ± 0.4	2.2 ± 0.7	1.6 ± 0.3 (n = 6)	1.9 ± 0.5	1.5 ± 0.5	3.4 ± 0.6*
UNa	20 ± 6 (n = 19)	20 ± 5	24 ± 6	48 ± 11*†	27 ± 15 (n = 6)	27 ± 14	35 ± 17	39 ± 17	18 ± 7 (n = 6)	24 ± 9	19 ± 10	68 ± 27*†
UK	49 ± 5 (n = 19)	50 ± 6	55 ± 6	67 ± 13	43 ± 10 (n = 6)	47 ± 10	65 ± 13	86 ± 42	52 ± 10 (n = 6)	59 ± 13	47 ± 12	63 ± 7
Ccre	94 ± 9 (n = 17)	75 ± 4	106 ± 12	101 ± 18	72 ± 6 (n = 5)	71 ± 6	139 ± 25	138 ± 58	85 ± 13 (n = 5)	72 ± 7	71 ± 12	75 ± 16
FENa	0.17 ± 0.05 (n = 17)	0.17 ± 0.04	0.17 ± 0.05	0.46 ± 0.14*†	0.28 ± 0.17 (n = 5)	0.20 ± 0.13	0.24 ± 0.12	0.38 ± 0.20	0.16 ± 0.07 (n = 5)	0.20 ± 0.06	0.16 ± 0.11	0.76 ± 0.4
PRA	— (n = 13)	—	22 ± 10	30 ± 16	— (n = 6)	—	12 ± 3	12 ± 3	— (n = 6)	—	14 ± 7	16 ± 6
Aldo	— (n = 15)	—	29 ± 7	27 ± 8	— (n = 7)	—	33 ± 10	16 ± 5*	— (n = 6)	—	29 ± 12	18 ± 8
NE	— (n = 16)	—	526 ± 121	417 ± 87*	— (n = 7)	—	295 ± 81	288 ± 88	— (n = 7)	—	600 ± 175	446 ± 133

* $p < 0.05$ vs preceding baseline; † $p < 0.05$ ANP vs placebo.
Values are mean ± standard error of the mean.
Aldo = plasma aldosterone concentration (ng/dl); PRA = plasma renin activity (ng/ml/hr); NE = plasma norepinephrine concentration (ng/liter); other abbreviations as in Table I.

cardial effects of anaritide in patients with heart failure indicates that it has no effect on contractility.[18]

Renal effects of atrial natriuretic peptide: Our study also demonstrates a favorable effect of anaritide infusion on some parameters of renal function in patients with heart failure. The changes in urine volume and in total and fractional excretion of sodium observed by Cody et al[3] were similar to those seen in our patients, but were not statistically significant in their small group of patients. Similarly, Saito et al[5] noted increases in urine volume and sodium excretion (as well as creatinine clearance) in their patients with heart failure, but the changes were not statistically significant. The modest improvement in parameters of renal function achieved statistical significance in our study because of the greater number of patients enrolled.

The magnitude of the response of renal function to ANP infusion in our patients is considerably less than that seen by Richards et al[1] in normal volunteers. They, however, used a single bolus of 100 μg, which makes

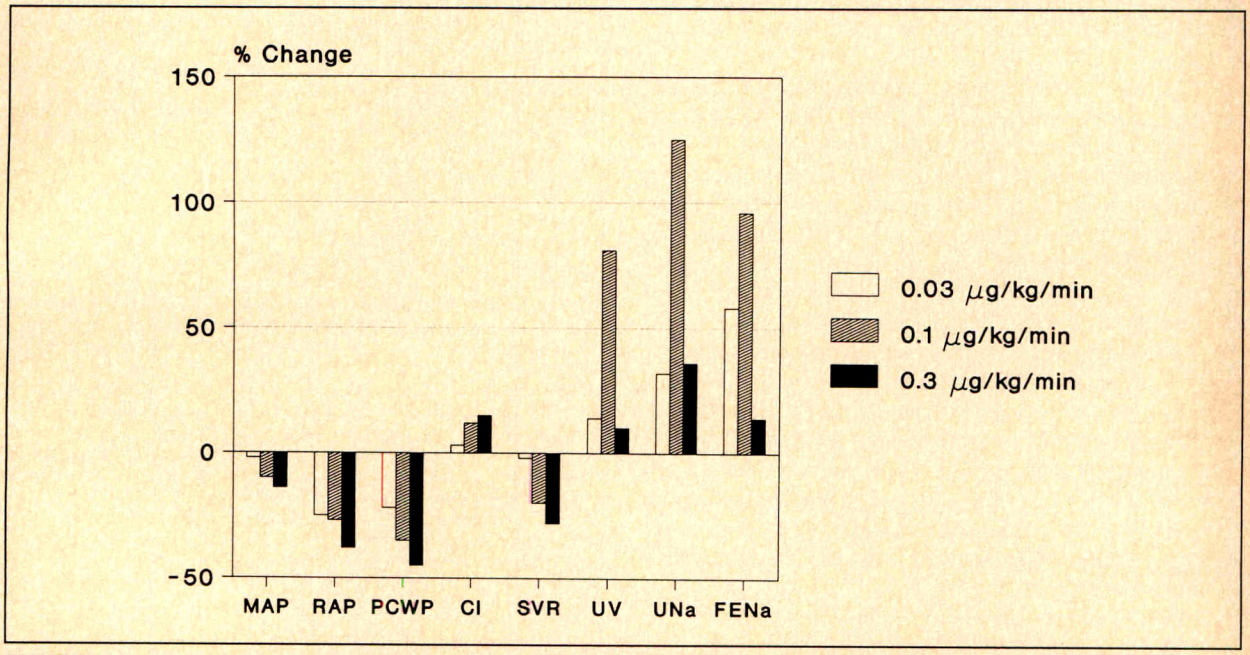


FIGURE 1. Percent changes in mean arterial pressure (MAP), right atrial pressure (RAP), pulmonary capillary wedge pressure (PCWP), cardiac index (CI), systemic vascular resistance (SVR), urine volume (UV), urinary sodium excretion (UNa) and fractional excretion of sodium (FENa) during initial 1-hour infusions of atrial natriuretic peptide according to dose administered. Indicated infusion rates apply to separate groups of patients, and thus do not provide a true dose-response relation.

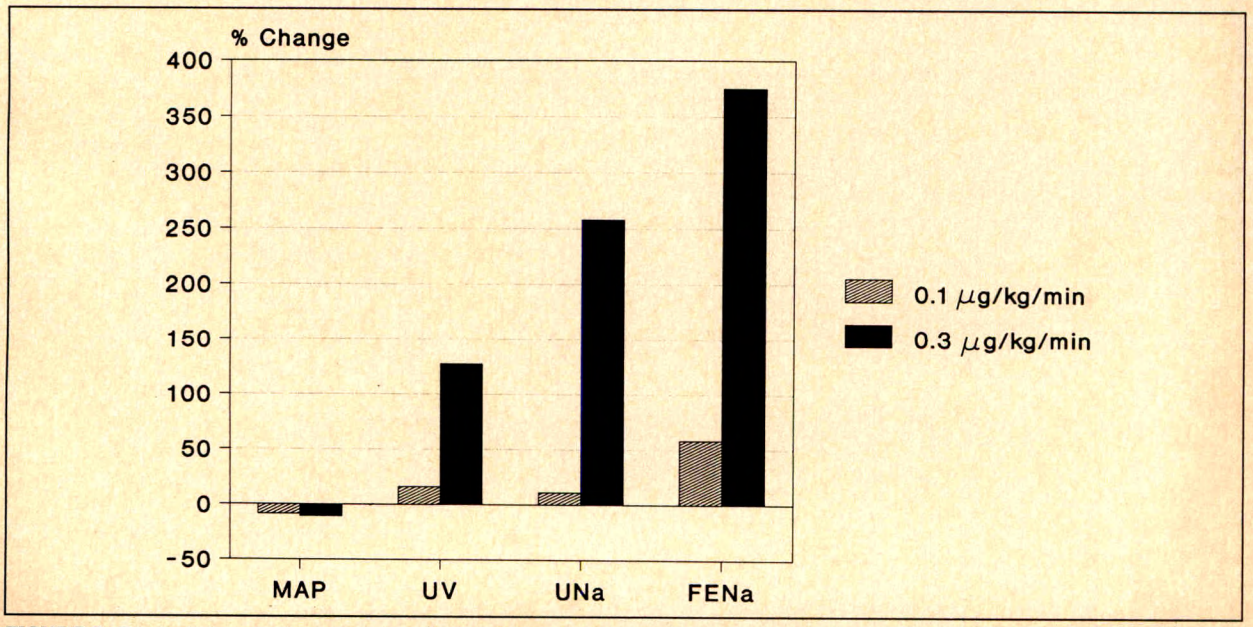


FIGURE 2. Percent changes in parameters during 2-hour infusions of atrial natriuretic peptide according to dose administered. Indicated infusion rates apply to separate groups of patients, and thus do not provide a true dose-response relation. Abbreviations as in Figure 1.

direct comparison difficult. The renal response of our patients to an infusion of 0.1 μg/kg/min is considerably less than that of the normal subjects studied by Cody,[3] Saito[5] and their co-workers to the same dosage. In our subgroup of patients receiving 2-hour infusions of 0.3 μg/kg/min, however, the magnitude of the increases in urine volume and sodium excretion is similar to the response to the lower dosage in the studies of Cody,[3] Saito[5] and their co-workers. This finding suggests that it may be possible to overcome renal hyporesponsiveness to ANP in patients with heart failure by the administration of a large dose of a synthetic analog of the hormone.

The reason for the greater response of renal parameters in patients receiving the initial 1-hour infusion of anaritide at a rate of 0.1 versus those receiving 0.3 μg/kg/min is not evident. Baseline ANP levels tended to be higher in patients receiving the higher infusion rate (140 ± 55 vs 65 ± 9 ng/dl, p = 0.07). Furthermore, mean systemic arterial pressure decreased by a slightly greater amount (14 vs 10%) to a slightly lower level (82 ± 5 vs 86 ± 3 mm Hg) in those receiving the higher rate. In this regard, a preliminary report has suggested that in patients with heart failure infusion of ANP at a very low rate may result in renal vasodilation and improvement in renal function without altering central hemodynamics.[19] It is possible, then, that diminished sensitivity to ANP or renal hypoperfusion contributed to this result. During 2-hour infusions, the response of patients receiving 0.3 μg/kg/min was greater than that of patients receiving 0.1 μg/kg/min.

Adverse reactions: Possible side-effects of anaritide were experienced by 17% (6 of 35) of the subjects, and were usually related to excessive reduction of systemic arterial pressure. Similar reactions were reported in 1 of 6 patients with heart failure[5] and 1 of 13 patients with hypertension.[17]

Limitations of the study: As discussed, a limitation of the present study is the inability to construct true dose-response relations for anaritide. Interpretation of Figures 1 and 2 must be qualified by this consideration. Furthermore, invasive measurements were not available during the 2-hour infusions. This study, nevertheless, provides the most comprehensive data regarding the effects of ANP in patients with heart failure available to date.

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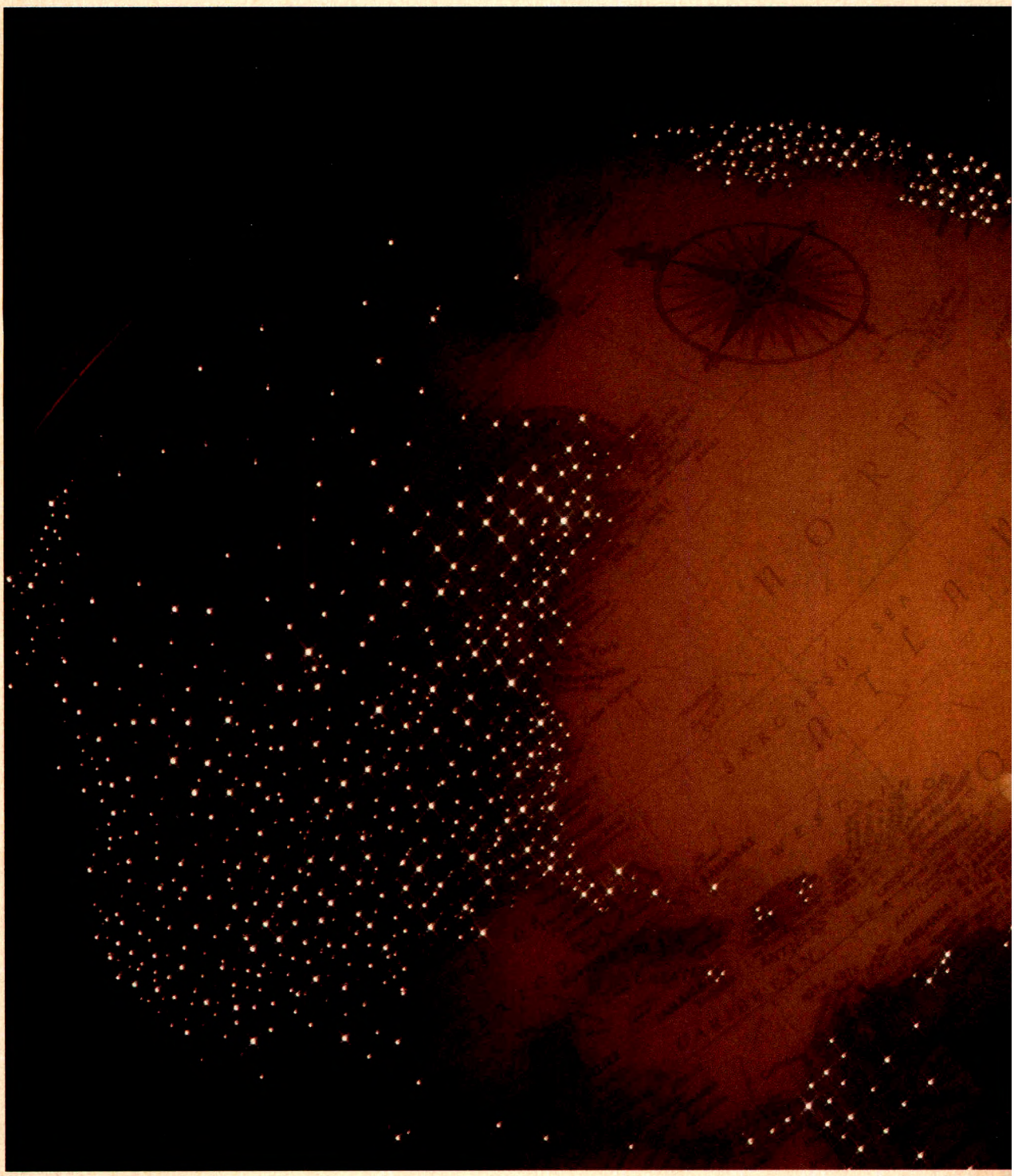
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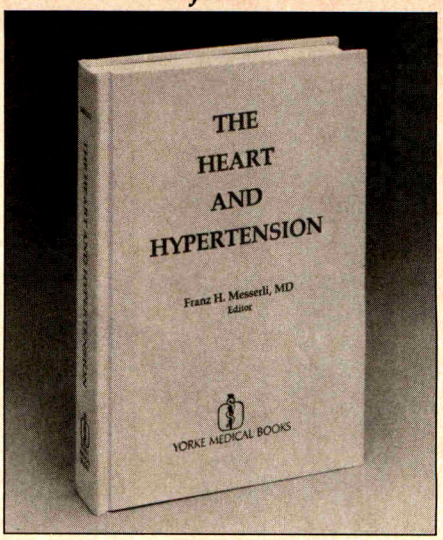
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Ten-Year Results with the St. Jude Medical Prosthesis

Chandra K. Nair, MD, Syed M. Mohiuddin, MD, Daniel E. Hilleman, PharmD, Richard Schultz, MD, Robert T. Bailey, Jr., PharmD, Cornelia T. Cook, BFA, and Michael H. Sketch, Sr., MD

Although the hemodynamic characteristics and durability of the St. Jude valve prosthesis have been reported, the need for and the degree of anticoagulation in patients who receive these valves remain uncertain. Our 10-year experience with 165 patients (100 men and 65 women, mean age of 58 ± 13 years), who underwent valve replacement with St. Jude prostheses, is reported. Of the 165 patients, 147 were treated with warfarin. A prothrombin time 1.3 to 1.8 times control (range 15 to 20 seconds) was maintained in 134 patients with single valve and 1.8 to 2 times control (range 20 to 25 seconds) in 13 patients with double valve prostheses. The 10-year actuarial event-free incidence from thromboembolic and hemorrhagic complications was 84 and 95%, respectively. Of the 8 patients receiving antiplatelet therapy alone, 4 had thromboembolic events. Of the 10 patients on neither warfarin nor antiplatelet therapy, 3 had thromboembolic events. The 10-year actuarial event-free incidence from valve failure was 95%. The 10-year actuarial patient survival was 55%. Thus, the St. Jude valve is a safe and reliable prosthesis with acceptable overall long-term performance in patients given a modest anticoagulation regimen. Patients who receive St. Jude prosthetic valves without anticoagulants have a high incidence of thromboembolic events despite therapy with antiplatelet agents.

(Am J Cardiol 1990;65:217–225)

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The St. Jude Medical valve prosthesis is made of durable thromboresistent pyrolytic carbon and is a bileaflet, low profile valve with central flow characteristics.[1–4] Compared with other mechanical prostheses, the St. Jude valve has a tilting disc with a superior effective orifice area that allows insertion of a hemodynamically favorable valve even in the presence of a relatively small recipient valve anular diameter. This may account for the favorable effective orifice area compared with valve size. This, in association with the low profile and central flow characteristics, makes the St. Jude valve hemodynamically closer to biologic valves.[5–8] However, a major difficulty associated with the use of nonbiologic valves is the increased incidence of thromboembolism and anticoagulation-related hemorrhage.[9–14] Although thromboresistant pyrolytic carbon does not completely avoid the use of anticoagulation, the types of antithrombotic agents and the degree of anticoagulation needed in patients with St. Jude prosthetic valves are still unresolved.[15–22] We report our 10-year experience with 165 patients who underwent St. Jude valve prostheses implantation.

METHODS

Study patients: From April 1978 through May 1987, 165 patients (100 men and 65 women), mean age 58 ± 13 (range 9 to 82) years, underwent valve replacement with St. Jude prostheses in St. Joseph Hospital, Creighton University. Of these, 93 were aortic, 59 were mitral and 13 were double (aortic and mitral) valve replacements. Thirty-one patients had concurrent myocardial revascularization. One-hundred and twelve (68%) had postinflammatory or degenerative valvular heart disease, 25 (15%) had coronary artery disease, 9 (5%) had congenital heart disease, 9 (5%) had endocarditis and 10 (6%) had valvular heart disease of uncertain etiology. Sixty (36%) had aortic stenosis, 45 (27%) had aortic regurgitation, 43 (26%) had mitral stenosis and 30 (18%) had mitral regurgitation as the predominant valvular lesion.

Surgery and anticoagulation: Surgical technique consisted of cardiopulmonary bypass with membrane oxygenation and systemic hypothermia (25 to 28°C). Potassium cardioplegia and topical hypothermia with ice cold saline were also used. All significant calcification was debrided from the native anulus. The prosthetic valves were fixed with interrupted mattress sutures with Teflon pledgets on the ventricular sides. The commonly used prostheses ranged from 23 to 25 mm sizes

TABLE I Frequency of Death and Other Complications in 165 Patients with St. Jude Valve Prosthesis and Subgroups by Valve Position and Antithrombotic or No Therapy

	Patients	Death		Thrombembolism	Hemorrhage	Valve Failure
		No.	%			
Valve position						
Aortic	93	10	11	7	3	2
Mitral	59	19	32	10	0	3
Double	13	3	23	1	2	0
Antithrombotic therapy						
Warfarin	123	20	16	10	4	3
Warfarin + dipyridamole	24	2	8	1	1	1
Aspirin + dipyridamole	8	3	38	4	0	0
No therapy	10	7	70	3	0	1
Total	165	32	19	18	5	5

for aortic and 27 to 31 mm sizes for mitral positions. Anticoagulation with warfarin was routinely started on postoperative day 2 to 4 with therapeutic levels achieved on the sixth to eighth postoperative day. Prothrombin times of 1.3 to 1.8 times control (15 to 20 seconds) were considered adequate anticoagulation for single valve prosthesis and 1.8 to 2 times control (20 to 25 seconds) for double valve prostheses. Prothrombin times were checked daily in the hospital, weekly until prothrombin time was relatively stable and then monthly thereafter. A total of 147 patients were maintained on warfarin. Of these, 24 patients were also receiving dipyridamole (225 mg daily in 3 equally divided doses) based on empirical decision by the personal physician or cardiologist. Of the 18 patients not given warfarin (because of lack of compliance or gastrointestinal bleeding), 10 took no

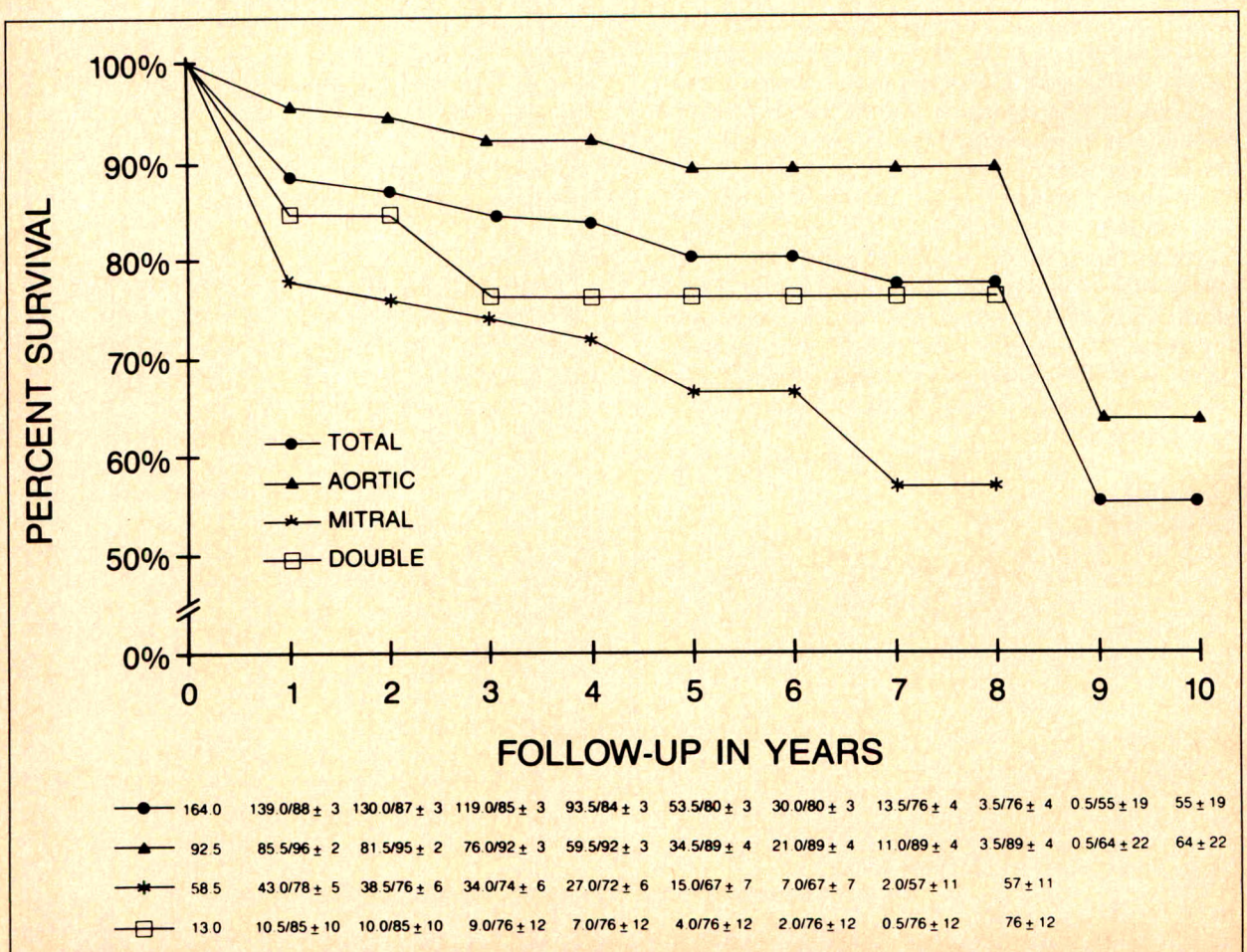


FIGURE 1. Actuarial survival for patients with St. Jude prosthesis. Aortic, mitral, double valve and total patients are shown.

anticoagulants or antiplatelet therapy and 8 took both aspirin (324 mg daily) and dipyridamole (225 mg daily in 3 equally divided doses) started within 2 to 3 days of surgery.

Long-term follow-up: Follow-up data were obtained by periodic evaluations in the outpatient clinic, reviewing the hospital records during hospitalizations and interviewing patients on the telephone or their families and personal physicians when deceased. Follow-up of hospital survivors ranged from 0 to 9.3 years (mean 4.3 ± 2.2). No patient was lost to follow-up. Ethical guidelines were used throughout the study by the investigators. All patients gave informed consent and the Institutional Committee on Human Research approved the study protocol.

Definitions: Thromboembolism included any new permanent or transient cerebrovascular or peripheral vascular embolic events in the absence of infection or another cause such as atrial myxoma and valve thrombosis confirmed by surgery, necropsy or both. Anticoagulation-related hemorrhage included all bleeding episodes resulting in death, stroke, change of medications, blood transfusion or hospitalization. Diagnosis of endocarditis required infection involving the prosthetic valve with combination of clinical signs (fever, new or altered cardiac murmurs, splenomegaly, systemic emboli or immunopathologic lesions), ≥2 positive blood cultures or positive histologic and microbial examinations of the explanted valves. Paravalvular leak was defined as a new aortic diastolic murmur or a new mitral systolic murmur detected by auscultation and confirmed by Doppler echocardiography, cineangiography or surgery. Valve failure was defined as mechanical valve dysfunction from valve disruption, breakage, leaflet dehiscence or valve thrombosis. Cardiac deaths included sudden and nonsudden deaths from cardiac causes. Sudden death was defined as cardiac death within 1 hour of onset of symptoms. Valve-related mortality included death caused by structural valve deterioration, nonstructural

TABLE II Summary of Frequency of Death and Other Complications in 165 Patients with St. Jude Valve Prosthesis

	Frequency		Percent Free from Events		
Event	No.	%	1 Year	5 Years	10 Years
Death	32	19	88 ± 3	80 ± 3	55 ± 2
Total complications*	28	17	95 ± 2	83 ± 3	76 ± 5
Thromboembolism	18	11	97 ± 1	88 ± 3	84 ± 4
Hemorrhage	5	3	99 ± 1	97 ± 2	95 ± 2
Valve failure	5	3	99 ± 1	97 ± 1	95 ± 2

* Only the first event was considered.
All ± data are mean ± standard error.

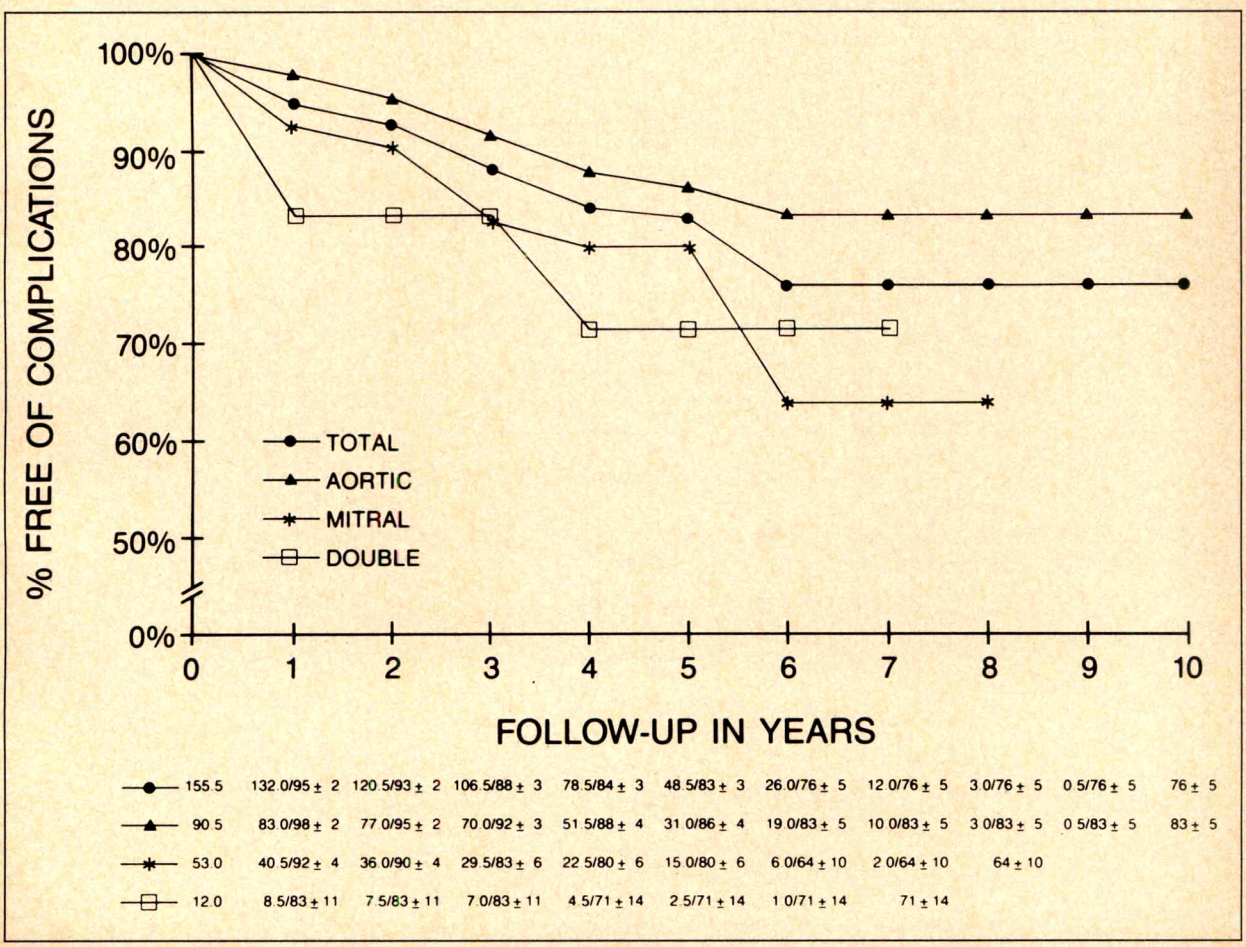


FIGURE 2. Actuarial freedom from complications for patients with St. Jude prosthesis. Aortic, mitral, double valve and total patients are shown.

valve dysfunction, thromboembolism, anticoagulant-related hemorrhage, prosthetic endocarditis or death at reoperation (deaths due to heart failure in patients with advanced myocardial disease and satisfactorily functioning prosthetic valves are not included). Operative mortality was defined as death during hospitalization for valve replacement or within 30 days of surgery if the patient had been discharged from the hospital before that time. All deaths occurring beyond the initial hospitalization for valve replacement or after the 30-day postoperative period if patients had been discharged were considered late deaths.

Statistical analysis: All data were analyzed using the statistical package for social sciences.[23,24] Unless indicated otherwise, values are mean ± standard deviation. Greenwood's formula and Kaplan-Meier plots were used to evaluate the 10-year actuarial rate of freedom from complications and actuarial patient survival. A p value <0.05 was considered significant.

RESULTS

Table I lists the frequency of death and other complications in total patients and subgroups in regard to the valve position and types of antithrombotic therapy or no therapy. Table II lists the results of survival analysis at 1, 5 and 10 years of follow-up with frequency of death and complications. Table III lists the clinical characteristics of patients with thromboembolic events after St. Jude prosthetic valve replacement. Of the 18 patients with thromboembolic events, 11 (7 mitral, 3 aortic and 1 double) were receiving warfarin (mean dose 4.7 ± 2 mg daily) and had a prothrombin time of 19 ± 3 seconds at the time of thromboembolic event. These values were 4.5 ± 2.8 mg daily and 20 ± 5 seconds, respectively, for the 136 patients taking warfarin without thromboembolic events. Of the remaining 7 patients with thromboembolic events, 4 (2 mitral, 2 aortic) were receiving combination antiplatelet therapy and 3 (1 mitral, 2 aortic) were not receiving warfarin or antiplatelet therapy. The mean age of the 18 patients with thromboembolic events was 59 ± 13 years compared to 58 ± 13 years for the 147 patients without thromboembolic events. Seven of 18 (39%) patients with thromboembolic events were in atrial fibrillation and 1 patient had paroxysmal supraventricular tachycardia. Twenty-six (18%) patients without thromboembolic events were in atrial fibrillation, 10 (7%) were in atrial flutter and 3 (2%) had paroxysmal supraventricular tachycardia. The clinical characteristics of the patients with hemorrhagic cerebrovascular events are listed in Table IV. Four of

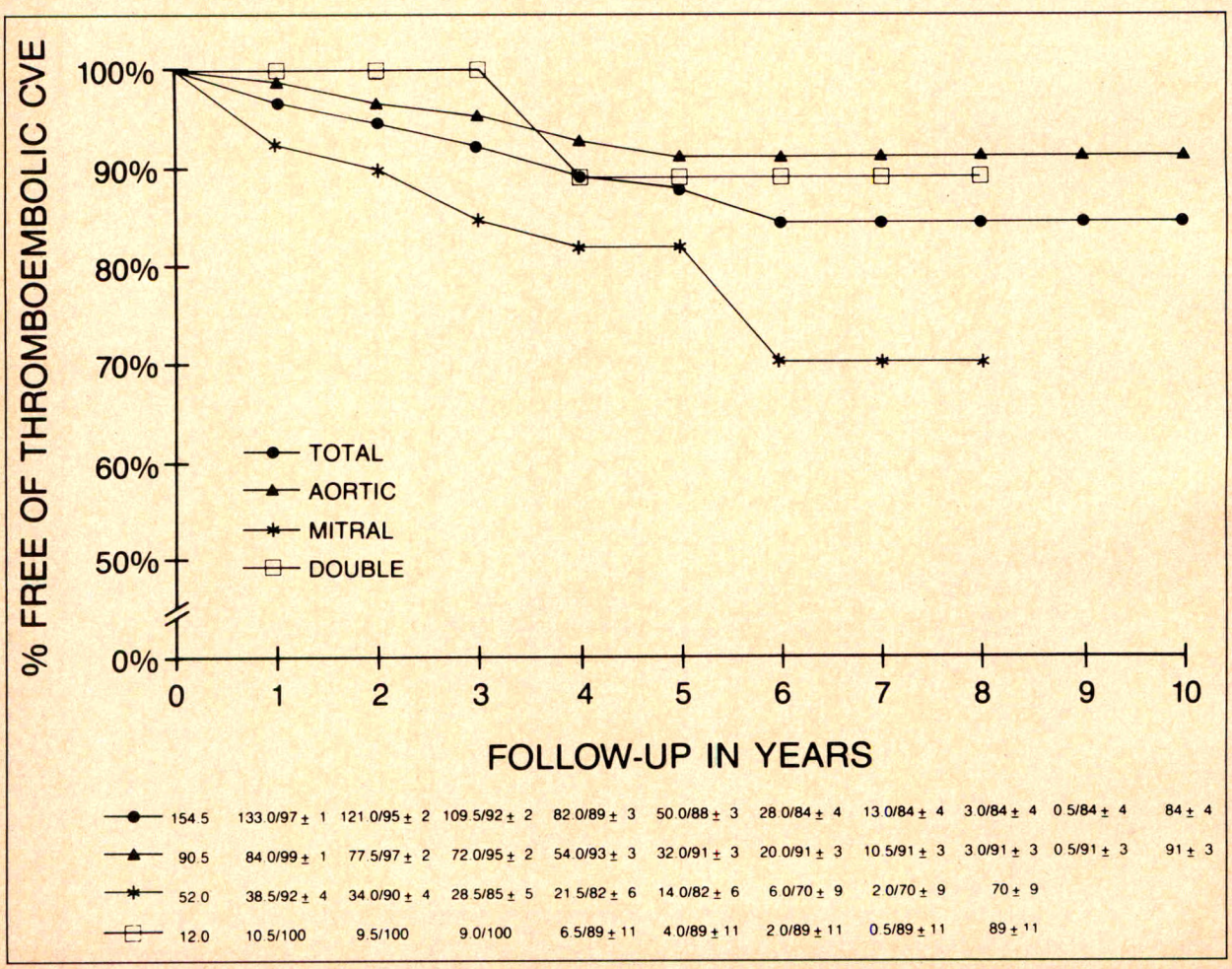


FIGURE 3. Actuarial freedom from thromboembolic cerebrovascular events (CVE) for patients with St. Jude prosthesis. Aortic, mitral, double valve and total patients are shown.

123 patients (3%) taking warfarin alone and 1 of 24 (4%) taking warfarin plus dipyridamole had a cerebrovascular hemorrhage during follow-up. The mean dosage of warfarin and the prothrombin time for the 5 patients with cerebrovascular hemorrhage was 4 ± 1 mg daily and 18 ± 6 seconds, respectively, compared to 5 ± 3 mg daily and 20 ± 5 seconds, respectively, for the remaining 142 patients taking warfarin. The mean age of the 5 patients with cerebrovascular hemorrhage was 63 ± 7 years compared to 58 ± 13 years for the 160 patients without cerebrovascular hemorrhages. The mean left atrial internal dimension on echocardiogram for the 142 patients without cerebrovascular events was 4.7 ± 1.2 cm; it was 5 ± 1 cm for the 23 patients with such events. Of these 23 patients, 18 with thromboembolic events had a mean left atrial internal dimension of 5 ± 1 cm compared to 4.5 ± 0.5 cm for the 5 patients with hemorrhage. There were no episodes of clinically detectable peripheral emboli or hemorrhage, paravalvular leak or endocarditis during the follow-up in any of the patients with aortic, mitral or double valve prostheses. The causes of death for total patients and those with aortic, mitral and double valve replacements are listed in Table V. Neither age nor sex was found to be a

TABLE III Clinical Characteristics of Patients with Cerebrovascular Thromboembolic Events After St. Jude Prosthetic Valve Replacement

Pt	Age (yrs), Sex	Location of Valve	Time after Surgery (mos)	Antithrombotic Therapy	Cardiac Rhythm
1	69, M	MV	11	O	SR
2	58, F	MV	33	W	SR
3	58, F	MV	66	W + D	SR
4	26, F	AV	9	W	AF
5	37, M	AV	43	A	SR
6	73, M	AV	28	O	SVT
7	68, M	MV	27	A	SR
8	69, M	AV	14	W	AF
9	65, F	DV	36	W	SR
10	58, F	MV	22	W	AF
11	54, M	AV	52	O	SR
12	67, F	AV	14	A	SR
13	64, M	MV	2	W	AF
14	65, M	MV	45	W	SR
15	51, M	MV	3	A	AF
16	67, F	MV	64	W	SR
17	65, F	MV	7	W	AF
18	43, M	AV	43	W	AF

A = antiplatelet therapy alone; AF = atrial fibrillation; AV = aortic valve; D = dipyridamole; DV = double valve; MV = mitral valve; SR = sinus rhythm; SVT = supraventricular tachycardia; W = warfarin.

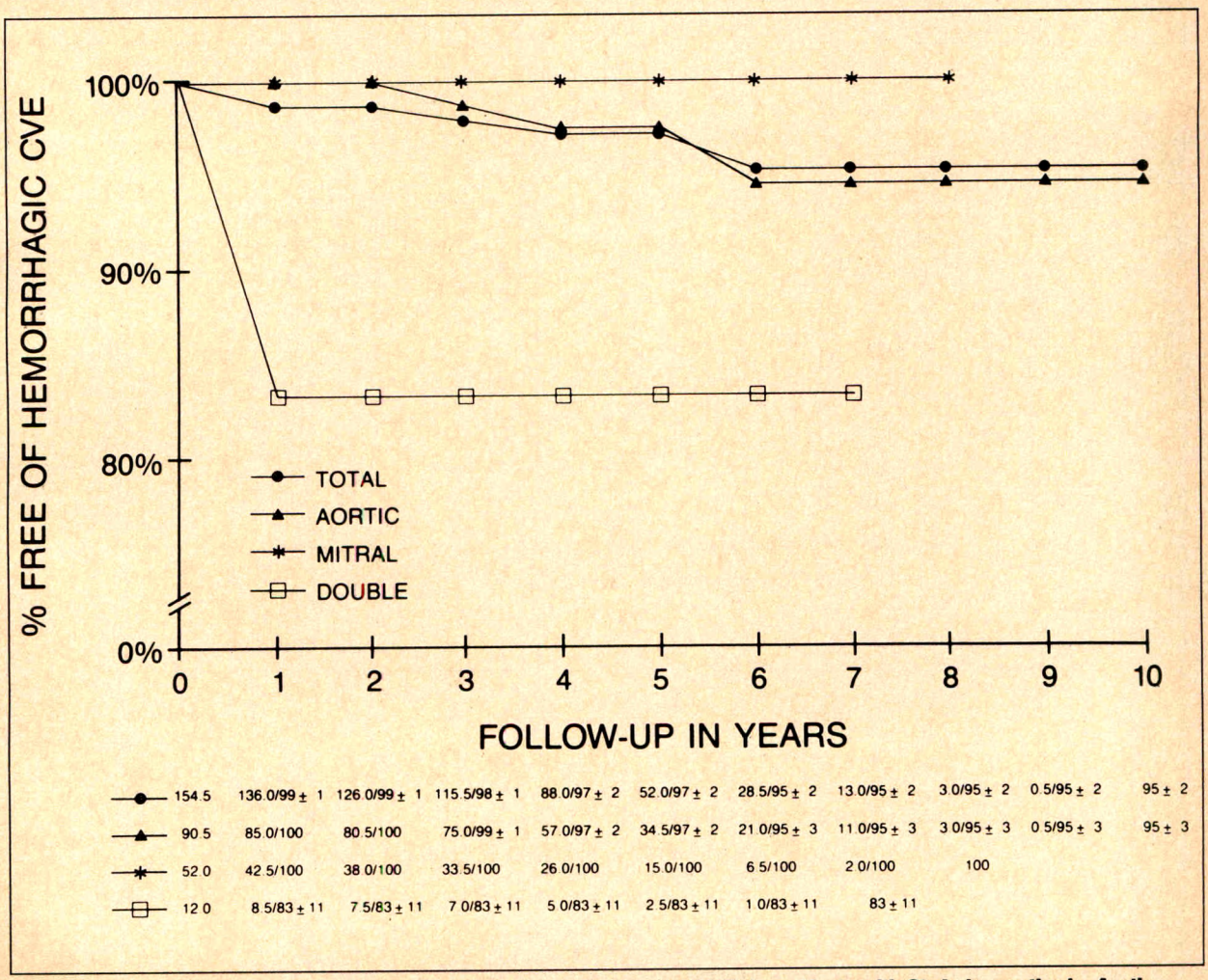


FIGURE 4. Actuarial freedom from hemorrhagic cerebrovascular events (CVE) for patients with St. Jude prosthesis. Aortic, mitral, double valve and total patients are shown.

TABLE IV Clinical Characteristics of Patients with Cerebrovascular Hemorrhagic Events After St. Jude Prosthetic Valve Replacement

Pt	Age (yrs), Sex	Location of Valve	Time after Surgery (mos)	Antithrombotic Therapy	Cardiac Rhythm
1	64, M	AV	28	W	AF
2	67, M	AV	37	W	SR
3	55, F	AV	66	W	SR
4	59, F	DV	3	W + D	AF
5	72, F	DV	6	W	AF

Abbreviations as in Table III.

significant prognostic factor for death or total complications. Actuarial survival rates and freedom from complications for patients with aortic, mitral, double valves and total patients are shown in Figures 1 to 4. Figures 5, 6 and 7 show actuarial rates of freedom from complications for different therapies or no therapy.

DISCUSSION

Valve-related complications and survival: The excellent hemodynamic characteristics and the durability of St. Jude prosthetic valve are well documented.[1–7] The 10-year actuarial event-free incidence from valve failure in this study was 95%. Valve failures were from valve immobility due to thrombosis and not due to structural defects. This supports the previous findings of the mechanical soundness of the St. Jude prosthetic valve.[5,20,25–27] The actuarial survival including operative mortality was 64% at 10 years for aortic, 57% at 8 years for mitral and 76% at 8 years for double valves; these compare favorably with previous reports for the St. Jude and other prosthetic valves. The actuarial freedom from complications was 83% for aortic, 64% for mitral and 71% for double valves at the latest follow-up. The overall actuarial patient survival and freedom from complications at 10 years were 55 and 76%, respectively. These data are also similar to previous reports for the St. Jude and other prosthetic valves.[8,19]

Anticoagulation and prothrombin time: The need for and the optimal anticoagulation regimen for patients with St. Jude prosthetic valves remain controversial. Pass et al[9] reported good results with no anticoagulation in a series of 34 children undergoing St. Jude prosthetic valve replacements but the follow-up was relatively short. McGrath et al[15] reported a significantly higher incidence of thromboemboli in children with St. Jude prosthetic valves receiving antiplatelet therapy alone

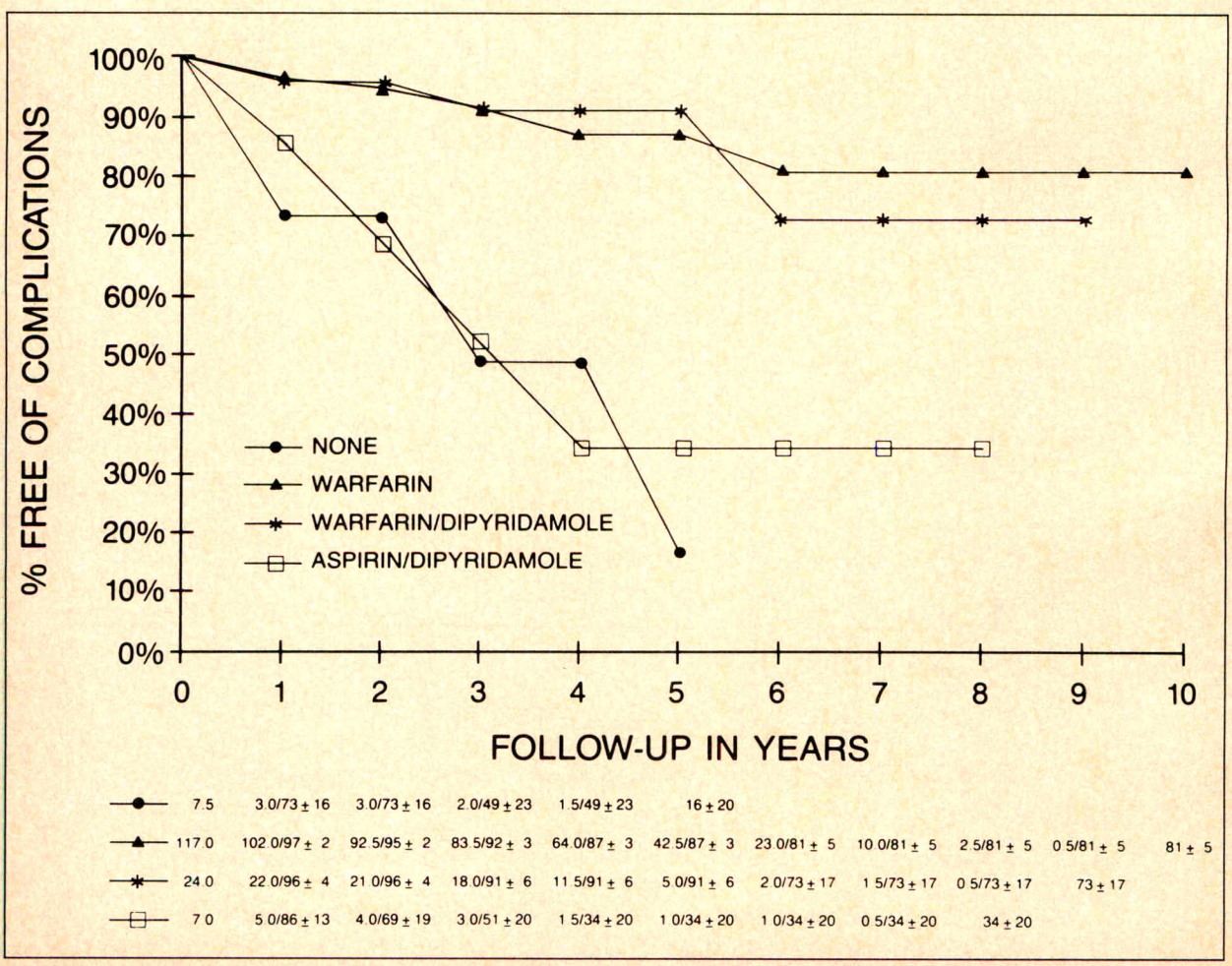


FIGURE 5. Actuarial freedom from complications for patients with St. Jude prosthesis treated with warfarin, warfarin and dipyridamole, aspirin and dipyridamole or no antithrombotic therapy.

and recommended full anticoagulation with warfarin in patients with St. Jude prosthetic valves. Baudet et al[16] reported a significantly higher incidence of valve thrombosis, systemic emboli and sudden death in a group of 78 patients with St. Jude prosthetic valves who were not anticoagulated compared to 630 patients receiving anticoagulation. Hartz et al[17] reported the incidence of thromboemboli in 83 patients with St. Jude prosthetic valves in the aortic position. Of these, 41 were receiving antiplatelet therapy alone and 42 were receiving warfarin anticoagulation. Four patients with valve thrombosis reported in this series were receiving antiplatelet drugs alone. Ribeiro et al[18] reported 5 cases of valve thrombosis among 67 patients with St. Jude prosthetic valves in aortic or aortic and mitral positions treated with antiplatelet therapy. This is also in agreement with the experience of Czer et al,[7] who reported 1.1%/patient-year incidence of thromboembolism in patients with St. Jude prosthetic valves treated with warfarin anticoagulation compared to 4.2%/patient-year among patients treated with antiplatelet drugs alone and 26.4%/patient-year in patients receiving neither anticoagulation nor antiplatelet agents.

All except 18 patients were receiving warfarin anticoagulation in our study. The prothrombin time was maintained in the range of 1.3 to 1.8 times control (15 to 20 seconds) with modest doses of warfarin except for 13 patients with double valves. The low rate of thromboembolism with modest doses of warfarin is similar to a recent report by Kopf et al,[26] who also demonstrated a low incidence of thromboembolism among patients with

TABLE V Causes of Death for Patients with Aortic, Mitral and Double Valves and Total Patients After St. Jude Prosthetic Valve Replacement

Cause of Death	Total Pts (n = 165)	Aortic (n = 93)	Mitral (n = 59)	Double (n = 13)
Operative mortality (%)	14 (7)	3	9	2
Congestive heart failure (%)	6 (4)	2	3	1
Sudden cardiac death (%)	4 (2)	2	2	0
Myocardial infarction (%)	2 (1)	2	0	0
Thromboembolic cerebrovascular event (%)	2 (1)	0	2	0
Repeat valve implant (%)	2 (1)	0	2	0
Noncardiac (%)	1 (1)	0	1	0
Unknown (%)	1 (1)	1	0	0
Total (%)	32 (20)	10	19	3

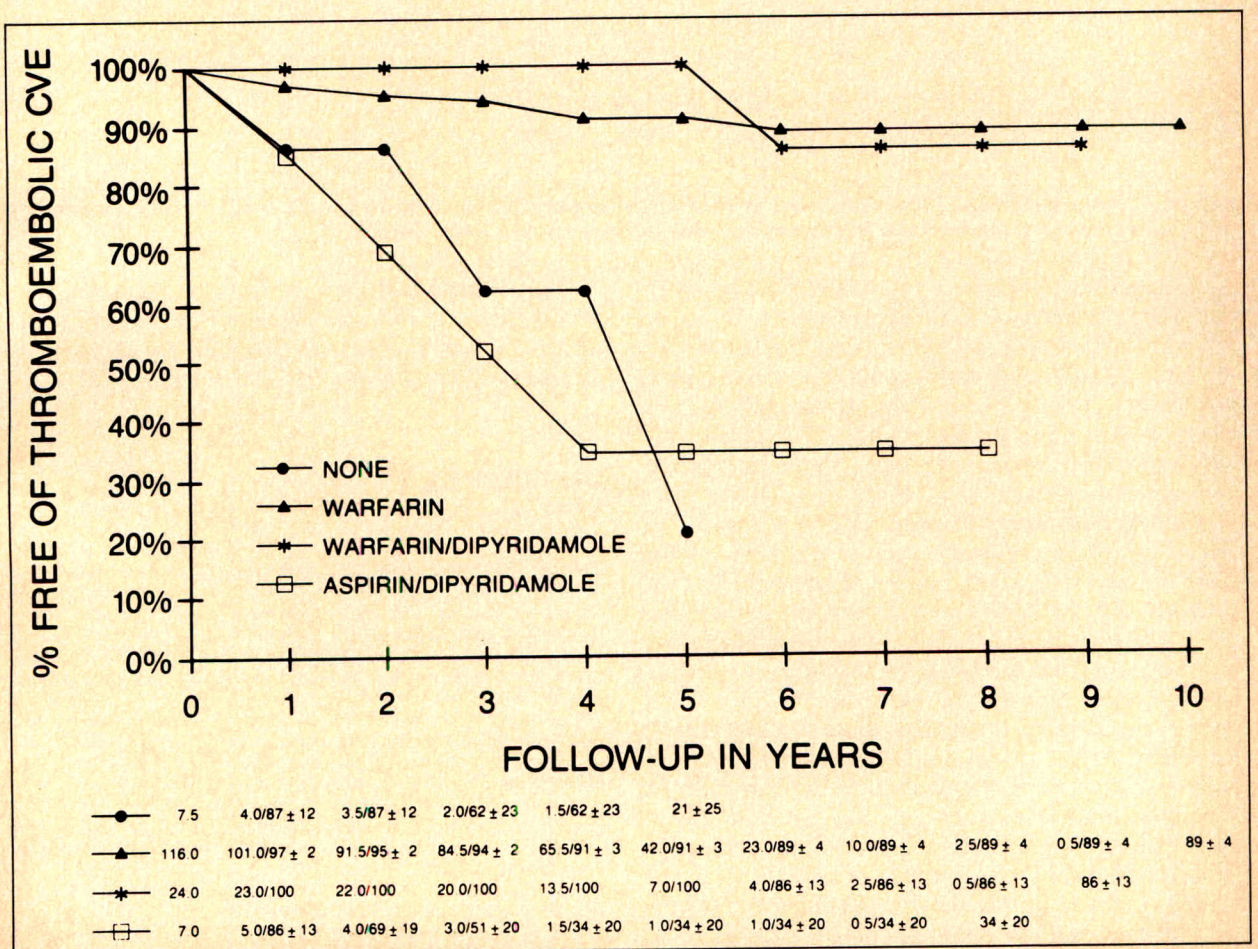


FIGURE 6. Actuarial freedom from thromboembolic cerebrovascular events (CVE) for patients with St. Jude prosthesis treated with warfarin, warfarin and dipyridamole, aspirin and dipyridamole or no antithrombotic therapy.

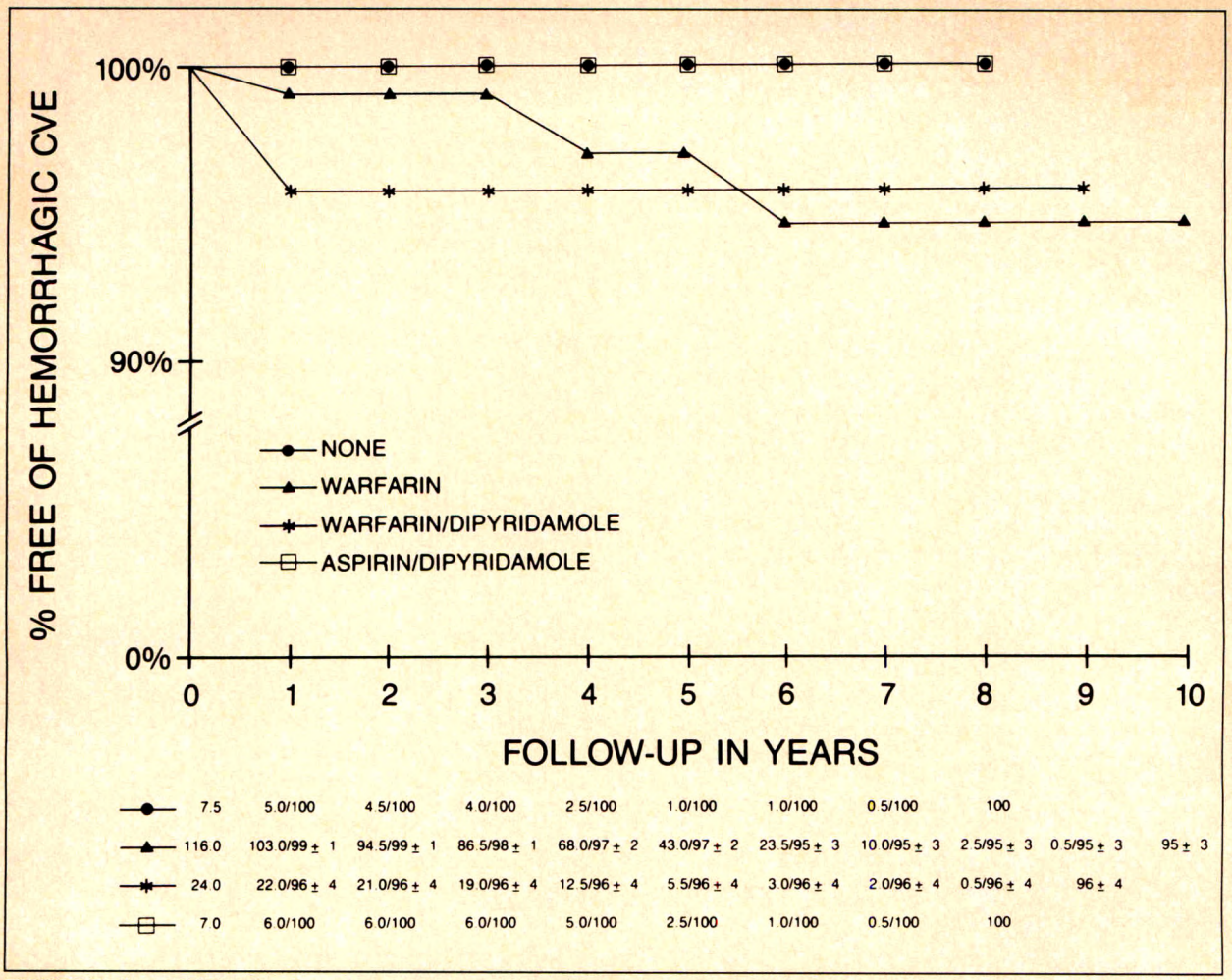


FIGURE 7. Actuarial freedom from hemorrhagic cerebrovascular events (CVE) for patients with St. Jude prosthesis treated with warfarin, warfarin and dipyridamole, aspirin and dipyridamole or no antithrombotic therapy.

St. Jude prosthetic valves given modest doses of warfarin. The incidence of anticoagulation-related hemorrhage in our study was low with this modest dose of warfarin. Patients with double prosthetic valves (mitral and aortic) in our study whose anticoagulation was maintained at 1.8 to 2 times control (20 to 25 seconds) with larger doses of warfarin had a higher incidence of anticoagulation-related hemorrhage.

Role of antiplatelet therapy: Of the 8 patients receiving antiplatelet therapy alone in our study, 4 had thromboembolic events and none had hemorrhagic complications. Of the 10 patients receiving neither warfarin nor antiplatelet therapy, 3 had thromboembolic events and none had hemorrhagic complications. Although small in numbers, pairwise comparison of thromboembolic complications show that these findings are in agreement with previous studies documenting the increased risk of thromboembolism in patients with St. Jude prosthetic valves receiving either antiplatelet therapy alone or no anticoagulant or antiplatelet therapy. More studies with larger numbers of patients seem indicated to evaluate further the role of antiplatelet therapy in addition to low dose warfarin anticoagulation to decrease the incidence of thromboembolism without increasing the risk of anticoagulation-related hemorrhage.

Acknowledgment: We express our appreciation to Wade Thomson, MS, and William P. Forbes, PharmD, for technical assistance, Ann Clark for secretarial assistance and Seamus Miau, MS, for statistical analysis.

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Assessment of Diastolic Filling Indexes Obtained by Radionuclide Ventriculography

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This study assesses how differences in residual volume and heart rate influence the measurement and interpretation of commonly used indexes of left ventricular filling obtained by radionuclide ventriculography. Thirty patients with hypertrophic cardiomyopathy (HC) and 26 normal subjects were studied. The time to peak filling rate (168 ± 42 vs 139 ± 35 ms; p = 0.006) and time to 30% filling (154 ± 32 vs 131 ± 29 ms; p = 0.009) were prolonged in patients with HC compared to normal subjects, suggesting impaired early diastolic filling. However the peak filling rate, measured in end-diastolic counts/s, was greater in patients with HC (3.31 ± 0.89 vs 3.06 ± 0.51, p = 0.19). This measurement was influenced by the relative residual volume (HC r = 0.41, p <0.001; normal r = 0.29, difference not significant), which was smaller in patients with HC (22.4 ± 8.0 vs 35.5 ± 5.6%; p <0.0001). The peak filling rate measured in stroke volume counts did not vary with the relative residual volume (HC r = 0.10, difference not significant; normal r = −0.21, difference not significant) and was less than normal in patients with HC (4.27 ± 0.69 vs 4.72 ± 1.0; p = 0.58). There was a strong association between the first third filling fraction and the heart rate (HC r = 0.66, p <0.001; normal r = 0.71, p <0.001), reflecting its dependence on the duration of the first third of diastole. The peak filling rate, measured in end-diastolic counts, and the first third filling fraction are poor measures of left ventricular filling because they are influenced by residual volume and heart rate, respectively.

(Am J Cardiol 1990;65:226–230)

Noninvasive techniques, including radionuclide ventriculography, pulsed Doppler ultrasound and M-mode echocardiography, have recently become more widely used to assess left ventricular (LV) diastolic function.[1] Abnormalities of LV filling have been identified in patients with coronary artery disease,[2–6] systemic hypertension,[7–10] hypertrophic cardiomyopathy (HC)[10–15] and with increasing age.[16,17] The reproducibility of indexes has been assessed[13,18] and indexes obtained by different techniques have been compared.[19–23] However, the root value of an index of diastolic function will depend on how sensitive it is to abnormal diastolic filling and whether it is influenced by factors other than LV filling, which would make interpretation difficult. This study assesses the value and limitations of several commonly used indexes of diastolic filling derived from the radionuclide time-activity curve in a group of normal subjects and a group of patients with HC.

METHODS

Radionuclide ventriculography was performed on 26 volunteers (mean age 39 years, range 22 to 68) who had no clinical or electrocardiographic evidence of cardiac disease and a normal blood pressure (<140/90 mm Hg) and 31 patients with HC (mean age 43 years, range 17 to 70). All subjects gave informed consent. The diagnosis of HC required evidence of LV hypertrophy without a physiologic stimulus for hypertrophy and was confirmed by electrocardiography and 2-dimensional echocardiography (maximum LV wall thickness >14 mm) in all patients. Seventeen patients had systolic anterior motion of the mitral valve. The mean maximum LV wall thickness was 19.6 ± 3.6 (standard deviation) mm.

Equilibrium gated blood pool ventriculography was performed at rest in the supine position, after in vivo labeling of red blood cells with technetium-99m. Images were acquired using a large field of view gamma camera oriented in the 45° left anterior oblique projection with caudal tilt to isolate the left ventricle. Data was acquired in list mode from 600 to 900 consecutive cardiac cycles. Cycles that were more than 20% from the mean cycle length were rejected. A background-corrected LV time activity curve was generated at a frame rate of 10 to 25 ms. The computer used a least-squares smoothing algorithm to obtain a smoothed curve and from this calculated the ejection fraction and indexes of diastolic filling.

The peak filling rate was calculated as the maximum rate of increase in counts during the passive phase of filling, measured in end-diastolic counts. The peak filling rate was measured in stroke volume counts/s by dividing the peak filling rate in end-diastolic counts/s

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TABLE I Diastolic Filling Indexes in Normal Subjects and Patients with Hypertrophic Cardiomyopathy

	Normal Subjects (n = 26)	HC Pts (n = 31)	Difference Between Means	95% Confidence Interval
Ejection fraction	35 ± 6	23 ± 8	13	9, 17
PFR (EDC/s)	3.06 ± 0.51	3.31 ± 0.89	0.25	−0.13, 0.63
PFR (SVC/s)	4.72 ± 0.69	4.27 ± 1.0	−0.45	−0.91, 0.02
Time to PFR (ms)	139 ± 35	168 ± 42	29	9, 50
Time to 30% filling (ms)	131 ± 29	154 ± 32	23	6, 39
First third filling fraction (%)	48 ± 19	41 ± 17	7	−3, 16

Data are mean ± standard deviation.
EDC/s = end-diastolic counts/s; HC = hypertrophic cardiomyopathy; PFR = peak filling rate; SVC/s = stroke volume counts/s.

by the ejection fraction. The time to peak filling rate was defined as the time from the minimum volume to the peak filling rate. The first third filling fraction was obtained by measuring the percent of the stroke volume in the left ventricle after one-third of the time between minimum volume and the subsequent R wave. The time to 30% filling was defined as the time from minimum volume to filling of the first 30% of the stroke volume (Figure 1).

Statistics: The mean and standard deviation, the difference between the means and the 95% confidence intervals of the differences between the means are given. The 95% confidence intervals were calculated using the unpaired 2-sample *t* test. The correlation coefficient was obtained using the BMDP statistical package and levels of significance estimated from the appropriate *t* tables. A p value >0.05 was regarded as not significant.

RESULTS

Influence of ejection fraction on peak filling rate measured in end-diastolic counts/s and stroke volume counts/s: The peak filling rate measured in stroke volume counts/s gave a lower measure than the peak filling rate in end-diastolic counts/s in patients with HC compared to normal subjects (Table I). This difference is accounted for by a larger ejection fraction in patients with HC ($p < 0.0001$) and is illustrated in Figure 2. The peak filling rate measured in end-diastolic counts/s was more strongly correlated with the ejection fraction in patients with HC who had a wider range of ejection fractions (normal, $r = 0.29$, difference not significant; HC, $r = 0.41$; $p < 0.001$). There was no significant association between the ejection fraction and the peak filling rate in stroke volume counts/s (normal, $r = -0.01$, difference not significant; HC, $r = 0.03$, difference not significant).

Influence of heart rate on diastolic filling indexes: There was a strong correlation between heart rate and the first third filling fraction (normal, $r = 0.71$, $p < 0.01$; HC, $r = 0.66$, $p < 0.01$). This can be accounted for by the strong correlation between the time for the first third of diastole and the heart rate (normal, $r = 0.703$, $p < 0.01$; HC, $r = 0.944$, $p < 0.01$). The regression equations for the first third filling fraction (y) and heart rate (x) were: normal, $y = 150 - 1.45x$, $r^2 = 0.464$; HC, $y = 101 - 0.91x$, $r^2 = 0.382$. The associations between heart rate and time to 30% filling (normal, $r = 0.08$, difference not significant; HC, $r = 0.36$, $p < 0.05$) and time to peak filling rate (normal, $r = -0.23$, difference not significant; HC, $r = 0.35$, $p < 0.05$) were weak (Figure 3).

Comparison of indexes of early diastolic filling: The mean time to peak filling rate ($p = 0.006$) and time to 30% filling ($p = 0.009$) were increased in patients with

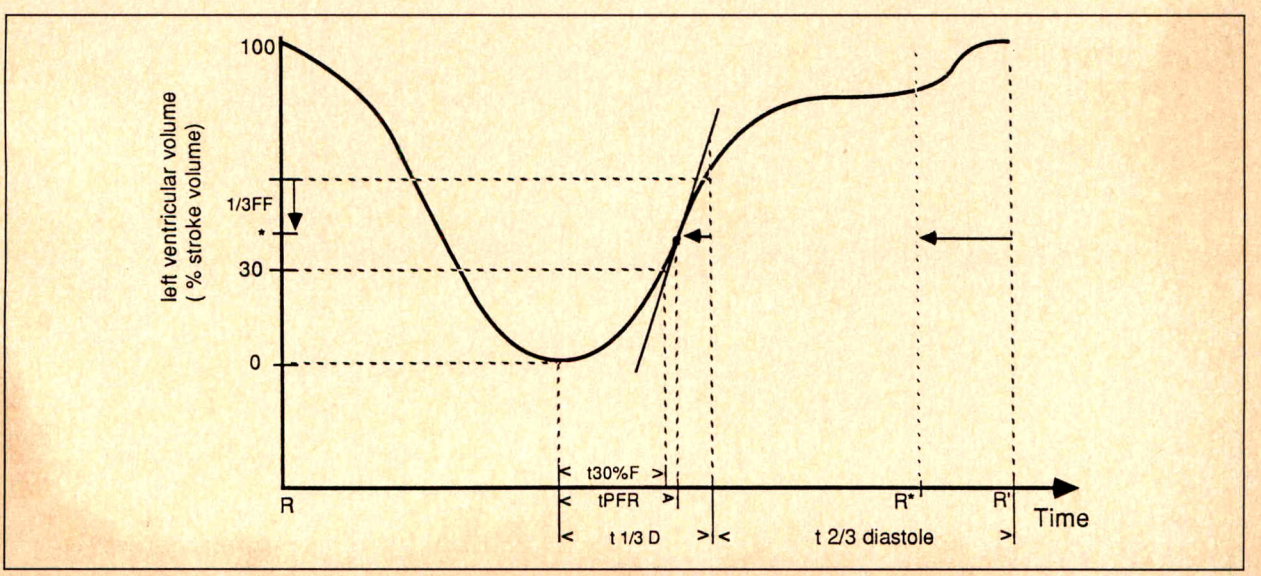


FIGURE 1. Measurement of indexes of early diastolic filling from the left ventricular time-activity curve. Note effect of change in heart rate from R to R* on the first third filling fraction (1/3FF), assuming no change in early diastolic filling. T 1/3D = time for the first third of diastole; t 30%F = time to 30% filling; t PFR = time to peak filling rate.

HC compared to normal subjects; this suggests impaired early diastolic filling (Table I). The peak filling rate measured in stroke volume counts/s was less in patients with HC but did not distinguish between normal subjects and patients with HC as clearly as the time to 30% filling or the time to peak filling rate (Table I). The increased mean peak filling rate measured in end-diastolic counts/s did not suggest impaired early diastolic filling in HC.

There was a close association between the time to peak filling rate and the time to 30% filling (normal, $r = 0.845$, $p < 0.01$; HC, $r = 0.944$, $p < 0.01$) but the first one-third filling fraction was more weakly associated with both these measurements (vs time to peak filling rate: normal, $r = -0.283$, difference not significant; HC, $r = -0.133$, difference not significant; vs time to 30% filling: normal, $r = -0.575$, $p < 0.01$; HC, $r = -0.278$, difference not significant) (Figure 4).

The time to peak filling rate occurred on average slightly later than the time to 30% filling (normal, 7.8 ms; HC, 14.5 ms) and the difference between these 2 times tended to increase as the average of the 2 times increased (normal, $r = 0.21$, difference not significant; HC, $r = 0.451$, $p < 0.01$) (Figure 5).

DISCUSSION

We have compared the sensitivity of different radionuclide indexes to impaired early diastolic filling, which has been well described in HC.[10–15] We have also assessed how differences in residual volume and heart rate influence commonly used indexes of diastolic filling. Patients with HC were slightly older and this may have contributed to the differences from the normal subjects.[16,17] An important limitation of this and other noninvasive studies of LV filling is the lack of an accepted "gold standard" against which different measurements can be compared. Invasive methods can be used to measure LV relaxation and stiffness, but the relation between these measurements and filling indexes has not been clearly defined.[1]

Differences in residual volume in patients with HC were associated with changes in the peak filling rate measured in end-diastolic counts/s but not the peak filling rate measured in stroke volume counts/s. Other in-

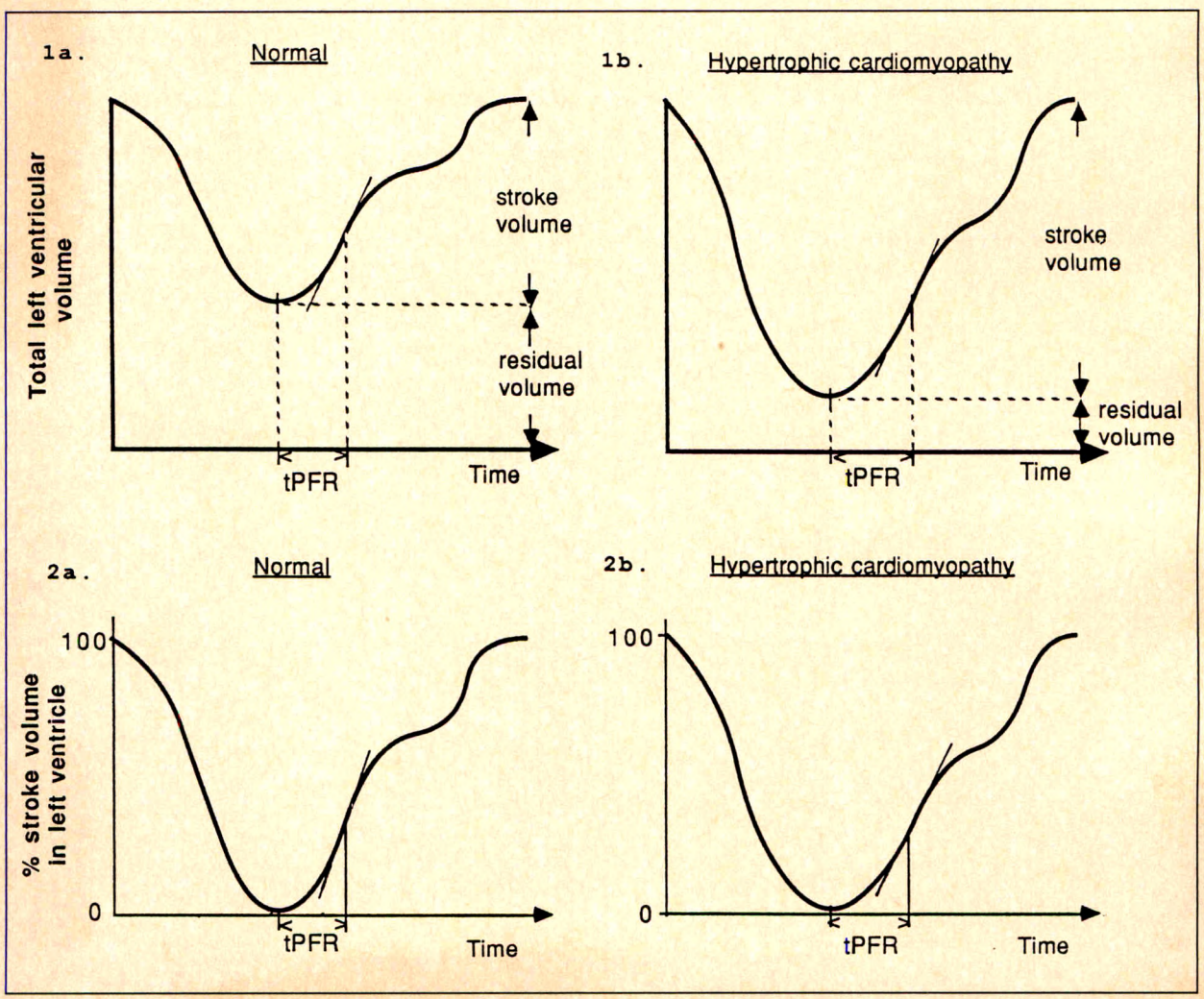


FIGURE 2. Left ventricular time-activity curves measured relative to end-diastolic left ventricular volume (*A1, A2*) and stroke volume (*B1, B2*) in a normal subject and a patient with hypertrophic cardiomyopathy (HC). The peak filling rate (PFR) appears to decrease in the patient with HC compared to the normal subject when it is measured relative to stroke volume.

vestigators[24] have also found an association between the peak filling rate measured in end-diastolic counts/s and the ejection fraction, a measure of relative residual volume. For this reason the peak filling rate measured in end-diastolic counts/s, which has been widely used as a measure of early diastolic filling, is difficult to interpret when comparing patients with different ejection fractions. This may also explain the poor correlation between the radionuclide peak filling rate measured in-end diastolic counts/s and the pulsed Doppler peak filling rate, despite a good correlation between other diastolic indexes measured using the 2 techniques.[21,23] The peak filling rate measured in stroke volume counts/s overcomes this limitation. Bowman et al[22] noted a good correlation between it and the peak filling rate standardized to stroke volume measured using pulsed Doppler ultrasound.

Although the accuracy of time measurements in radionuclide ventriculography is limited by the frame rate, the time to peak filling rate and the time to 30% filling were the most sensitive indexes of abnormal early diastolic filling in HC. The peak filling rate measured in

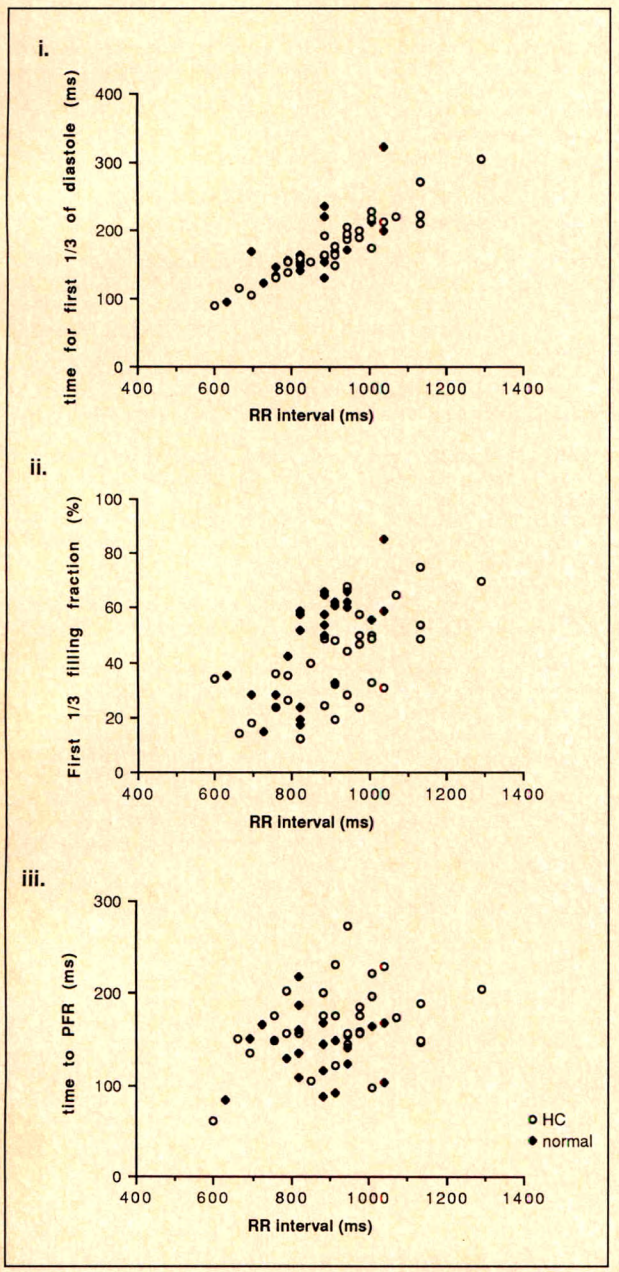


FIGURE 3. Relation between heart rate (measured as RR interval) and the time for the first third of diastole (*i*), the first third filling fraction (*ii*), and the time to peak filling rate (PFR) (*iii*). Note that the mean first third filling fraction is greater in normal subjects than patients with hypertrophic cardiomyopathy (HC), but the individual values are strongly influenced by the RR interval.

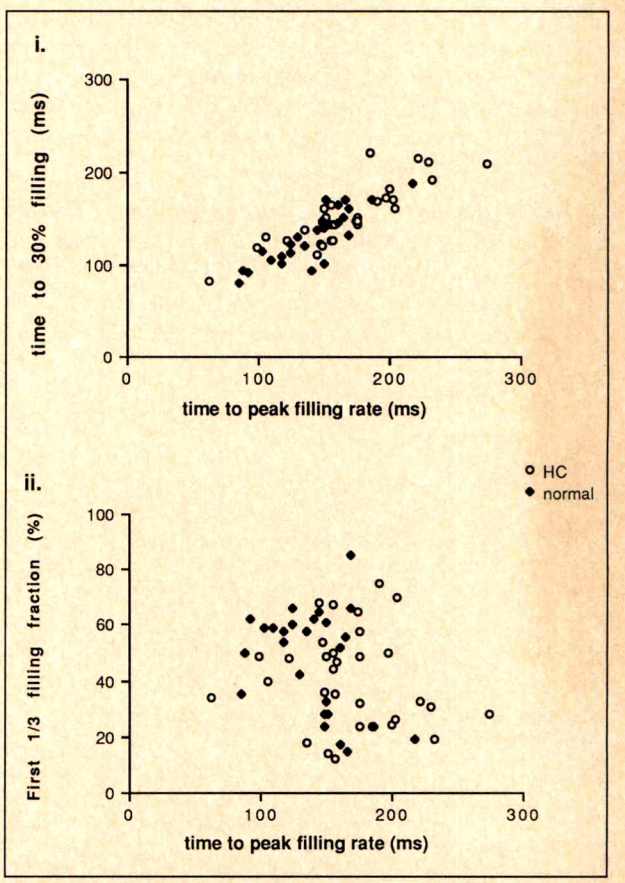


FIGURE 4. Relation between the time to peak filling rate and the time to 30% filling (*i*), and the first third filling fraction (*ii*).

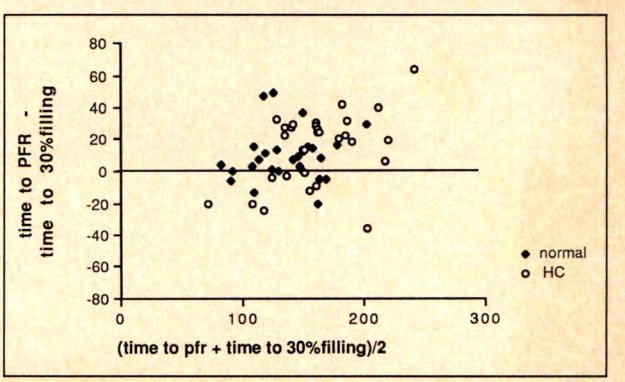


FIGURE 5. Comparison of the time to peak filling rate (PFR) and the time to 30% filling. Note that the time to PFR is on average slightly longer than the time to 30% filling and this difference tends to increase as the time required for early filling increases (the average of the 2 measurements is plotted).

stroke volume counts/s may be less sensitive because of its dependence on stroke volume and preload,[25] which may be increased in patients with HC who often have mitral regurgitation.[15]

The strong dependence of the first third filling fraction on the heart rate limits its value and this cannot be easily overcome by dividing the index by the RR interval. This simple correction[3,7] does not take into account slowing of filling after the peak filling rate and the nonlinear relation between the heart rate and the duration of diastole.[26]

These findings cannot necessarily be extended to other diseases in which the relation between diastolic indexes, ejection fraction and heart rate could be different. However, the findings suggest that the influence of factors other than LV filling should be considered when interpreting commonly used radionuclide indexes of "diastolic function."

Acknowledgment: We acknowledge the technical assistance of Shaughan Dickie, Melvyn J. Meyers and J. Peter Lavender, and thank Dr. Celia Oakley for support and critical review of the manuscript.

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Characteristics and Natural History of Abnormal Atrial Rhythms in Left Isomerism

Kazuo Momma, MD, Atsuyoshi Takao, MD, and Toshimitsu Shibata, MD

The object of this study is to document variation in atrial pacemaker rate and P-wave axis, and to clarify the natural history of abnormally slow atrial rhythms in left isomerism. Standard 15-lead electrocardiograms of 50 patients with left isomerism were retrospectively studied. On the average, 9 electrocardiograms covering 7 years for each patient were available. For comparison, atrial rhythms in patients with right isomerism and in those with situs solitus and 5 representative congenital cardiac conditions were studied with the same study protocol.

In left isomerism, atrial rhythm with constantly normal P-wave axis was exceptional and the presence of atrial rhythm with abnormal P-wave axis was the rule. The most frequent abnormal mean frontal P-wave axis was between −30 and −90°, recorded in 70%. Slow atrial rates below the second percentile were observed in 50%, either transiently and recurrently (in 40%), or persistently (in 10%), and were associated with junctional escape in 42%. The number of patients with slow atrial rate increased with age. In right isomerism, multiple atrial rhythms were also frequent, but slow atrial rhythm was present in only 4%. Multiple atrial rhythms or bradycardia associated with junctional escape were rare in the group of patients with congenital heart disease and situs solitus. It is concluded that multiplicity and progressive slowing of the atrial rhythm are characteristic in patients with left isomerism.

(Am J Cardiol 1990;65:231–236)

Atrial and pulmonary isomerism form an anomaly complex characterized by bilateral left-sidedness, usually with polysplenia.[1–3] Associated cardiac anomalies are variable and often complex.[3,4] Histologic studies in the last decade have revealed ectopic location and hypoplasia of atrial nodal tissue in left isomerism.[5–7] Corresponding to these histologic abnormal locations of atrial nodal tissues, electrocardiograms in left isomerism have revealed multiple atrial rhythms with abnormal P-wave axes.[8,9] Association of left isomerism with atrioventricular block has been well documented.[10] However, the complex nature of atrial rhythms in left isomerism remains to be fully clarified. This study documents variations of P-wave rates and axes in a large number of patients with left isomerism, and clarifies the relation between atrial pacemaker rate and age.

METHODS

Electrocardiograms of 50 patients with left isomerism were reviewed retrospectively. These were consecutive patients (32 males, 18 females) who were admitted to this institute from 1983 to 1987. Follow-up ranged from 0 to 19 years. All patients had routine cardiac studies including echocardiography and cardiac catheterization. All patients had intracardiac anomalies as listed in Table I. In all 50 patients, left pulmonary isomerism was diagnosed by chest radiograms[4] and selective pulmonary artery angiography.[11] This diagnostic criterion consists of bilateral presence of anatomic left pulmonary artery and bronchus (hyparterial bronchus). Howell-Jolly bodies were not found in the peripheral blood of any patient. Multiple spleens were noted on technetium-99m scintigraphy of the spleen in 13 patients. In the remaining patients, splenic scintigrams were not available. Multiple spleens were confirmed by autopsy in another patient.

Four hundred fifty electrocardiograms were reviewed, an average of 9 electrocardiograms/patient covering a period of 7 years. These electrocardiograms were recorded without any premedication with 6-channel recorders and paper speed of 25 mm/s. Usually patients were fully awake during the recording. About 10 heart beats were recorded in each lead. Six limb leads or V_1 through V_6 chest leads were recorded simultaneously, and made it possible to analyze ectopic atrial pacemakers and P-wave axis in those patients with wandering or shifting pacemakers. Electrocardiograms after intracardiac surgery, during digitalis therapy or after administration of drugs were excluded from the analysis. In each electrocardiogram, P waves were checked for morphology, PR interval, atrial rate and mean P-

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TABLE I Associated Anomalies in 50 Patients with Left Isomerism

Anomalies	Pts (n)
Position of heart and stomach	
Levocardia and left-sided stomach	21
Levocardia and right-sided stomach	14
Dextrocardia and left-sided stomach	9
Dextrocardia and right-sided stomach	6
Connections of venae cavae to atria	
Bilateral superior venae cavae to ipsilateral atria	18
Azygos or hemiazygos connection of inferior vena cava (others are shown in Figure 3)	34
Atrial septum	
Atrioventricular septal defect or common atrium	43
Secundum atrial septal defect	4
Intact atrial septum	3
Type and mode of atrioventricular connection	
Type of connection	
Biventricular heart with right-hand pattern	22
Biventricular heart with left-hand pattern	16
Double inlet right ventricle	9
Double inlet left ventricle	3
Mode of connection	
Common valve	34
Two perforate valves	16
Ventricular septum in 38 biventricular hearts	
Intact ventricular septum	1
Ventricular septal defect	9
Atrioventricular septal defect-partial	4
Atrioventricular septal defect-complete	34
Ventriculo-arterial junction	
Pulmonary artery	
Pulmonary atresia	5
Pulmonary stenosis	26
No pulmonary stenosis, no pulmonary hypertension	2
No pulmonary stenosis, pulmonary hypertension (origin of aorta in 38 biventricular heart)	17
From left ventricle	15
From right ventricle in double-outlet right ventricle	20
From right ventricle in levo-transposition	3

wave frontal axis. Atrial and ventricular rates were calculated from 6 successive intervals in limb leads and 6 intervals in chest leads.

Atrioventricular block was present in 25 (50%) of 50 patients; 15 had first-degree block, 6 had second-degree block and 4 had third-degree block. In 13 of these 25 patients, progression of atrioventricular block was documented during the course of observation. We analyzed P waves and atrial rhythms regardless of the presence or absence of atrioventricular block.

Mean frontal axis of the P wave was calculated with standard methods.[12] P waves whose mean frontal axis differed by >60° were diagnosed as indicating differing atrial origin. Those rhythms with abnormally short PR intervals were included in junctional rhythm. Normal ranges of the PR interval and P rate in children were adopted from published reports.[13] Slow atrial rate is defined by P rate below 2 percentiles for age. For young adults over 16 years, heart rates <60 beats/min were defined as slow, because this is the lower limit of normal heart rate in adolescents.[12,13]

For comparison with left isomerism, atrial rhythms of patients with right isomerism and those of 5 patients with congenital heart diseases with situs solitus were studied with the same protocol. These included 50 patients with right isomerism, 50 patients with small ventricular septal defects, 50 patients with tetralogy of Fallot including 22 patients with pulmonary atresia, 14 patients with atrioventricular septal defect, 20 patients with congenitally corrected transposition of the great arteries and 16 patients with double-outlet right ventricle.

RESULTS

Multiple atrial rhythm: Patients with abnormal atrial rhythms in each group are shown in Table II. In left isomerism, atrial rhythms with P axis >+90° or <0° were common; they were present in 49 of 50 patients, with only 1 patient showing persistent atrial rhythm with normal P axis. Multiple atrial rhythms were also common and were present in 34 of 50 patients with left isomerism (Figure 1). Usually these rhythms appeared on different occasions in the out-patient clinic. The

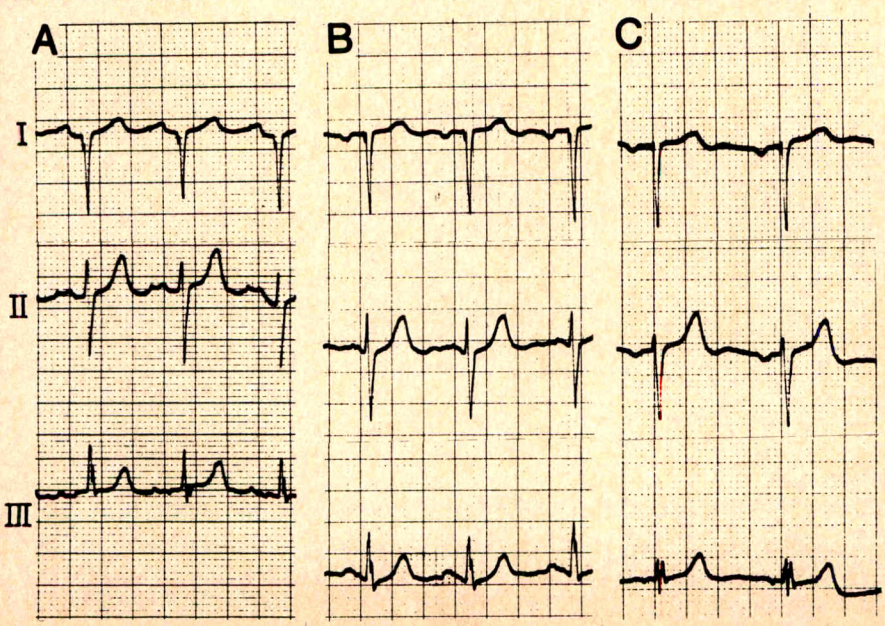


FIGURE 1. Three different P waves recorded on different days in a 6-year-old boy with left isomerism. Associated cardiovascular anomalies included levocardia (A,D,D), left-sided superior vena cava, left-sided inferior vena cava connected to hemiazygos vein, common atrium, common atrioventricular valve, double outlet right ventricle, ventricular septal defect and pulmonary stenosis. P wave axes in these electrocardiograms (paper speed 25 mm/s) were +40° (*A*), +140° (*B*) and −140° (*C*).

TABLE II Numbers of Patients with Abnormalities of Atrial Rhythms in Left and Right Isomerism and Five Other Congenital Heart Diseases with Situs Solitus

	Left Isomerism (n = 50)	Right Isomerism (n = 50)	VSD (n = 50)	T of F (n = 50)	Endocardial Cushion Defect (n = 16)	Double-Outlet Right Ventricle (n = 17)	Congenitally Corrected Transposition (n = 20)
Mean age (yrs)	7.4	7.0	10.6	3.4	15.1	6.1	10.2
Range	0–33	0–29	0–39	0–45	0–45	0–14	0–32
ECGs/patient	9.0	10.1	7.6	6.2	6.2	10.1	11.5
Slow atrial rate (%)	25 (50)	2 (4)	10 (20)	7 (14)	1 (7)	3 (18)	3 (15)
Transient	20	0	10	7	1	3	3
Persistent (%)	5	2 (4)	0	0	0	0	0
Junctional escape (%)	21	2 (4)	0	1	0	0	1
Multiple atrial rhythms (%)	34 (68)	37 (74)	3 (6)	1 (2)	1 (7)	1 (7)	6 (30)
P-wave axis (%)							
0 to 90°	18 (36)	40 (80)	50 (100)	50 (100)	16 (100)	17 (100)	20 (100)
>90 or <0°	49 (98)	54 (108)	3 (6)	0	1 (7)	0	6 (30)
−1 to −90°	35	4	1				2
91 to −91°	30	47 (94)	2		1		4

ECGs = electrocardiograms; T of F = tetrology of Fallot; VSD = ventricular septal defects.

numbers of the atrial rhythms in each patient were 1 in 16, 2 in 23, 3 in 9 and 4 in 2 patients, with an overall average of 1.94 different atrial rhythms/patient.

The mean frontal P-wave axis in these patients was distributed in a wide range as shown in Figure 2. Values for children under 1 year were plotted in a central circle. Atrial rhythm with axis between −30 and −90° was the most frequent rhythm; it was observed in 35 patients.

The relation of these atrial rhythms and patterns of the connections of both caval veins to the atria are shown in Figure 3. Some correlations between laterality of caval connection and P-wave axes were noticed. That is, in those patients in which both cavae connected to the right side of the atria, 80% of P waves showed axis between +90, 0 and −90°, as shown in the 4 left cavo-atrial patterns in Figure 3. In contrast, in those patients in which both cavae connected to the left side of the atria, P wave axes distributed evenly. Bilateral superior venae cavae were associated with right and left atrial rhythm with equal frequency.

In 5 patients with congenital heart diseases and situs solitus, atrial rhythms other than normal sinus rhythm were rare (Table I). Low right atrial or left atrial rhythms were observed transiently in those patients who had normal sinus rhythm on other occasions. In right isomerism, multiple atrial rhythms were documented in 74%. However, superiorly oriented P-wave axes were rare, as listed in Table II.

Atrial pacemaker rate: Slow atrial rhythm was observed in 25 of 50 patients with left isomerism, transiently and recurrently in 20 and persistently in 5 patients. Chronologic study of electrocardiograms in each individual revealed a definite tendency toward progressive slowing of atrial rate in these patients. Slow atrial rhythm transmitted to the ventricle without junctional escape in 4 patients as shown in Figure 4, but in the remaining 21 patients, junctional rhythm took place as an escape rhythm. The ages of patients with transient and recurrent slow atrial rate ranged from neonate to 15 years (average 5 years). The ages of the 5 patients with persistent slow atrial rate ranged from 2 to 33 years (average 8). In 2 of these 5 patients, initial transient slow atrial rate changed to persistent slow atrial rate, one at 3 years and another at 6 years of age. In no instance was tachyarrhythmia associated with these slow atrial rates. Fourteen unselected patients were followed from 0 to at least 5 years of age and their atrial rates are plotted in Figure 5. In at least 3 patients, slow atrial rate developed between 2 and 8 years of age.

Age distribution of slow atrial rates of these 50 patients is shown in Figure 6 (which also includes data from patients in Figure 5). Patients with recurrent tran-

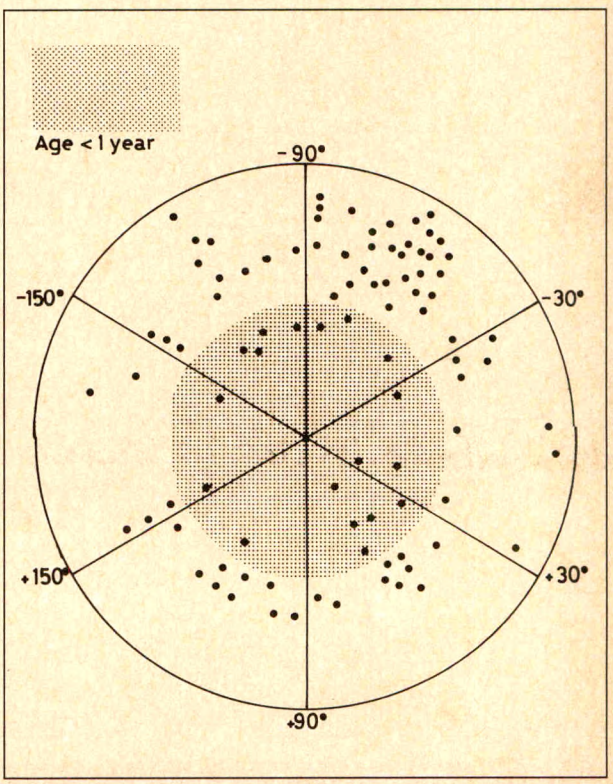


FIGURE 2. Mean frontal plane axis of P wave in left isomerism. Those under the age of 1 year are shown in the central circle (*shaded area*). P-wave axis is distributed widely, and axes between −30 to −90° are most frequent.

TABLE III Numbers of Atrial Rhythms in Patients with Left Isomerism with Normal Atrial Rate or Slow Atrial Rate

No. of Atrial Rhythms in Each Pt	1	2	3	4
With normal atrial rate (n = 26)	12	11	2	1
With slow atrial rate (n = 24)	4	12	7	1
Total (n = 50)	16	23	9	2

sient slowing of the atrial rate were also included in the slow group. Patients were divided into 5 age groups. Many patients spanned 2 or more age groups in the course of this study. If 1 patient had both normal and slow atrial rate in the same age range, this patient was counted as having slow atrial rate. Figure 6 shows a definite tendency for development of slower atrial rates as age advances. Slow atrial rate was observed in 22% under age 1 year, with an increase to 65% between 15 and 30 years of age. Junctional rhythm without identifiable P wave appeared as an escape mechanism in these 21 patients with slow atrial rate, persistently in 4 and transiently in 17 patients. The rates of the junctional rhythm were below the second percentile of the normal sinus rates[13] and between 48 and 65/min in 17 patients. In the remaining 4 patients, the rates of the junctional rhythm were between 65 and 100/min, and these correspond to the second to twenty-fifth percentile of the normal rate.[13]

To see the effect of multiple atrial rhythms on slowing of the atrial pacemaker, the numbers of P waves in patients with consistently normal atrial rates and those with slow atrial rates are listed in Table III. Most patients with slow atrial rate had 2 or 3 different P waves.

Slowing of the P waves was rare in right isomerism; it was observed in only 2 of 50 patients (Table II). In 5 patients with congenital heart diseases and situs solitus, sinus bradycardia below the second percentile was occa-

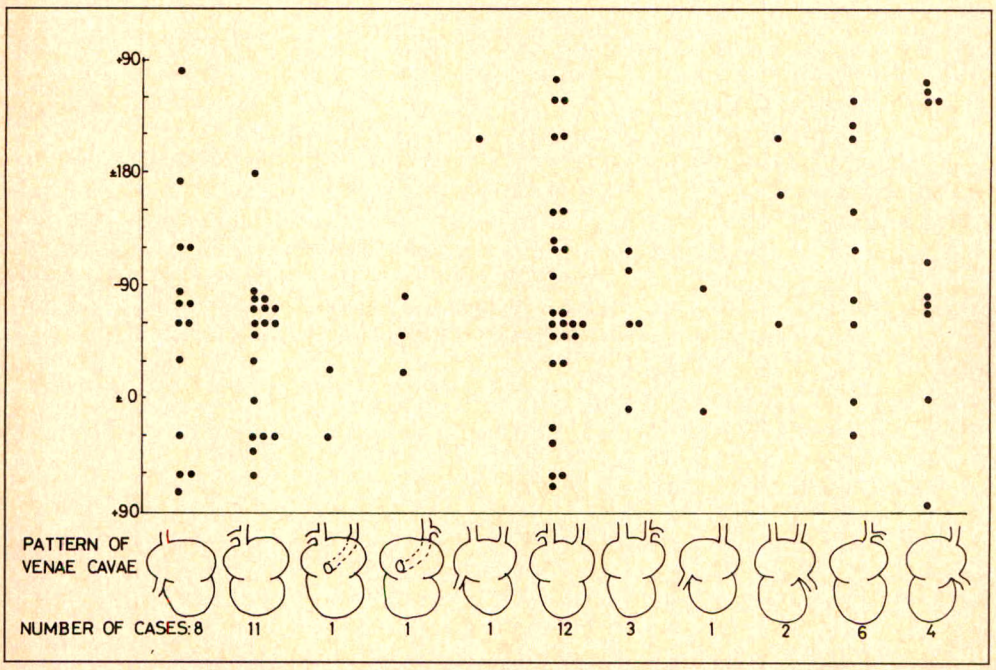


FIGURE 3. Mode of connection of venae cavae to the atria and mean frontal plane axis of the P wave.

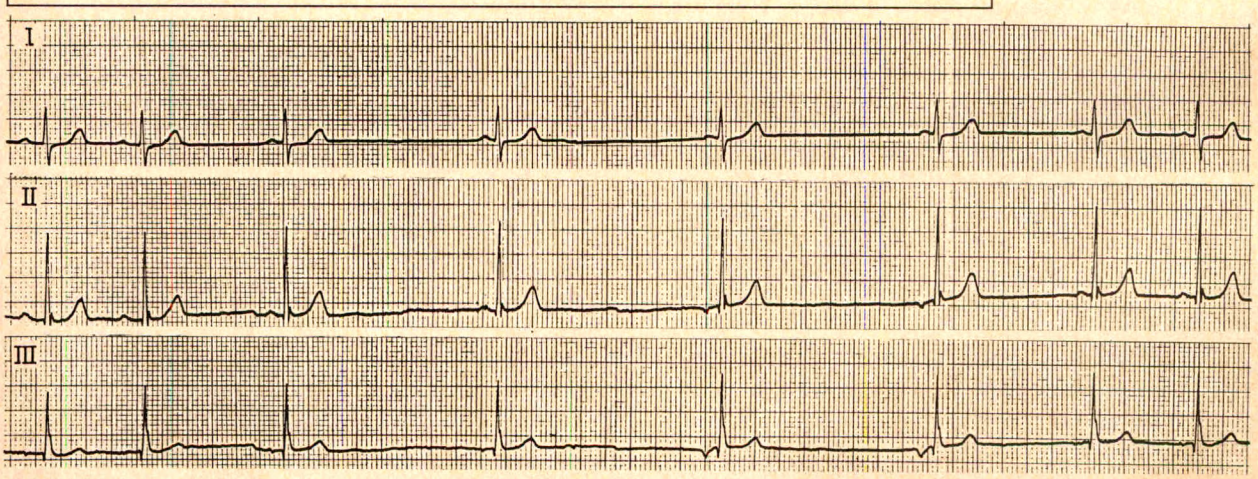


FIGURE 4. Transient slow atrial rate associated with change of frontal mean axis of P wave in 13-year-old girl with left isomerism. Paper speed was 25 mm/s. Associated anomalies were limited to azygos connection of inferior vena cava and persistent left superior vena cava draining to the coronary sinus. Sinus node recovery time, estimated by electrophysiologic study in the catheterization laboratory, was prolonged to 5,400 ms.

sionally observed. Sinus bradycardia was most frequent between 7 and 14 years, and at these ages, 25% of patients with ventricular septal defect or tetralogy of Fallot showed sinus bradycardia on some occasion. However, the degree of bradycardia was generally mild in these patients with situs solitus, and junctional escape was seen only rarely, in contrast to the usual association of junctional rhythm in slow atrial rate of left isomerism.

Symptoms: Symptoms directly related to slow atrial rates were not observed in any patients. One patient with both slow atrial rate and advanced atrioventricular block developed Adams-Stokes attack due to transient ventricular tachycardia at age 8 years, and received an artificial pacemaker. Congestive heart failure might be aggravated by bradycardia due to slow atrial rate in these patients, but was never related solely to atrial slow rate.

DISCUSSION

During the last decade, studies of atrial conduction tissue in left isomerism have revealed that sinus node tissue is located not in the normal position, but in the lateral atrial wall[4,5] near the ostium of the coronary sinus,[6] or in the right upper and left upper atrial walls.[7] In this study, multiple atrial rhythms with various P-wave axes were present in patients with left isomerism, suggesting the presence of multiple pacemaker tissue in both right and left sides of the atria or at several craniocaudal levels of atria in the same individual. The exact location of the individual atrial rhythm in left isomerism remains to be determined.

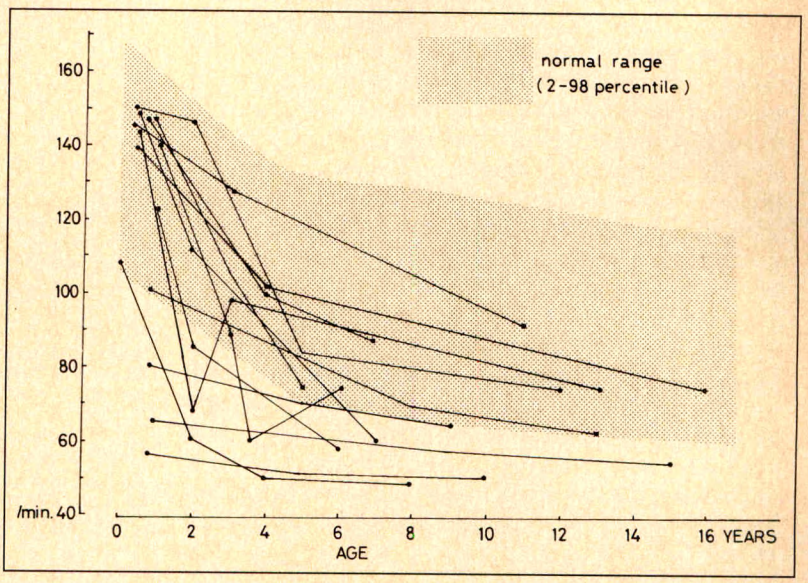


FIGURE 5. Atrial rates in 14 patients with left isomerism who were followed from infancy up to 5 years or more. Normal range (2 to 98 percentiles) is shown (*shaded area*). In 3 or 4 cases, slow atrial rate developed between 2 to 8 years of age.

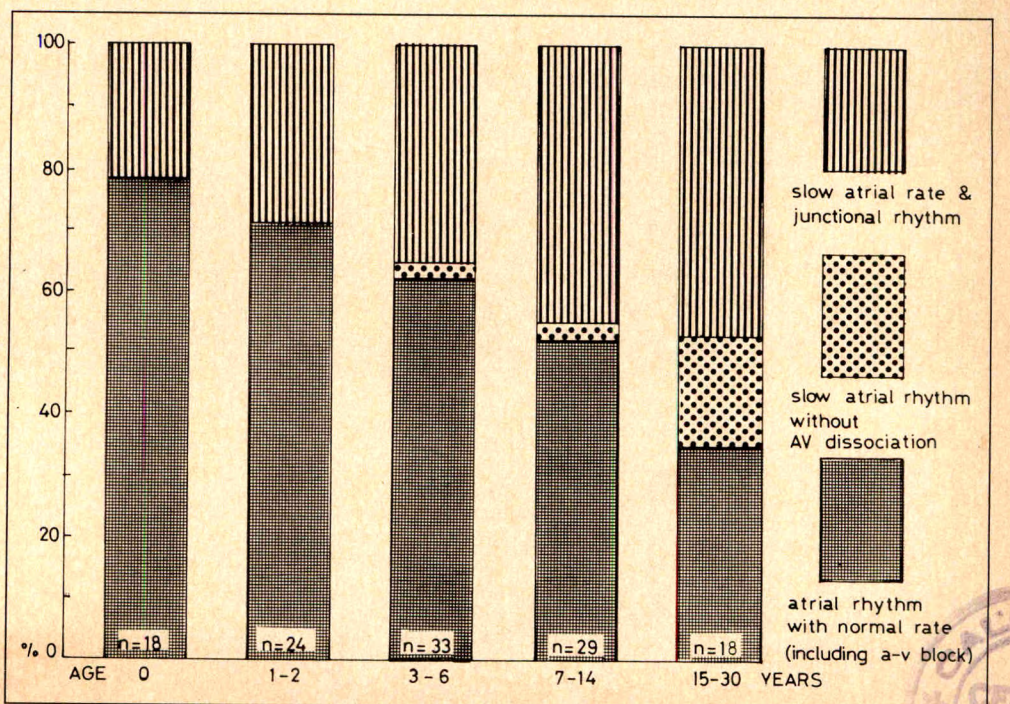


FIGURE 6. Frequency of slow atrial rate in left isomerism in 5 age groups. The number of patients with slow atrial rates increased progressively with age.

Recent histologic studies have shown hypoplasia of ectopic sinus nodes in left isomerism.[4,5] In some patients, hypoplasia was so extreme that sinus node tissue was not recognized in serial sections cut every 0.5 mm.[5] These histologic findings correspond with the progressive slowing of atrial rhythms in left isomerism in the present study. In several histologic studies in adults with sinus node dysfunction, the most constant findings were decrease in sinus node cells and increase in fibrosis of the atrial wall.[14–16] Decrease in sinus node cells is common in sinus node dysfunction in adults and in slow atrial rhythms in children with left isomerism.

The reason that slow atrial rhythms were not noticed in early studies seems 2-fold. One is the mild and transient slowing of the atrial rhythm in left isomerism. In a recent report by Wren et al,[10] prolonged atrial pauses were recorded during sleep in 2 patients with left atrial isomerism. These 2 patients appear to belong to the same category as those with slow atrial rate in our study. In many patients in our study, slow atrial rhythm and junctional escape were transient and asymptomatic. Another reason that slow atrial rates have been missed may be related to its slowly progressive course. We studied a large number of patients in later childhood and in young adulthood. In contrast, usually only 1 electrocardiogram was studied in each patient, and at an early age, in earlier reported studies.[8–10]

Established abnormalities in left isomerism include abnormal P-wave axis[8] and occasional atrioventricular block.[10] The present study has shown that slow atrial rate associated with junctional escape is another electrocardiographic finding with left isomerism. These slow atrial rates and junctional escape are transient in many patients and can be missed easily. However, these electrocardiographic abnormalities may be the first clinical clue enabling early recognition of the diagnostic possibility of left isomerism.

Acknowledgment: Editorial help of Leonard M. Linde, MD, Professor of Pediatrics, University of Southern California School of Medicine, is highly appreciated.

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Doppler Echocardiographic-Determined Changes in Left Ventricular Diastolic Filling Flow Velocity During the Lower Body Positive and Negative Pressure Method

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Changes in parameters of left ventricular (LV) diastolic filling flow obtained with Doppler echocardiography during the lower body positive and negative pressure method were analyzed in 15 patients (12 with coronary artery disease and 3 with dilated cardiomyopathy). Lower body pressure was altered at 5 steps (+20, +10, 0, −20 and −40 mm Hg vs atmospheric pressure). Pulmonary capillary wedge pressure measured with a ballon-tipped catheter was changed proportionally with lower body pressure during the procedures ($p < 0.01$). Mean systemic arterial pressure was changed slightly during lower body positive pressure and negative pressure of −40 mm Hg. Heart rate was almost unchanged except at lower body pressure of −40 mm Hg. The peak velocity of LV early diastolic filling flow was changed with pulmonary capillary wedge pressure in an almost parallel fashion during the procedures ($p < 0.01$). The peak velocity of LV late diastolic filling flow showed smaller changes than that of early diastolic filling flow. Changes in pulmonary capillary wedge pressure correlated positively with changes in the peak velocity of LV early diastolic filling flow ($r = 0.759$, $p < 0.01$), but not with changes in the peak velocity of LV late diastolic filling flow ($r = 0.039$, not significant) during lower body negative pressure of −20 mm Hg. These data suggest that left atrial pressure is one of the important determinants of LV early diastolic filling flow in this acute clinical setting and that LV late diastolic filling flow is less sensitive to changes in left atrial pressure than LV early diastolic filling flow.

(Am J Cardiol 1990;65:237–241)

Parameters of left ventricular (LV) diastolic filling have often been used to assess LV diastolic properties,[1–3] particularly to estimate the rate of LV isovolumic relaxation.[4–6] On the other hand, both experimental[7,8] and clinical[9–12] studies suggested an important role of left atrial pressure in LV diastolic filling dynamics. Although the quantitative relations between left atrial pressure and parameters of LV diastolic filling have been examined extensively in the experimental settings,[7,8] they remain to be elucidated in patients. Lower body negative pressure method has been reported to reduce venous return in a stepwise manner.[13] Left atrial pressure can also be decreased stepwise during this procedure. By contrast, lower body positive pressure method can increase left atrial pressure by augmenting venous return. Using both these methods, it seems possible to control left atrial pressure stepwise in a wide range. Accordingly, we analyzed changes in parameters of LV diastolic filling flow, obtained with pulsed Doppler echocardiography, and those in hemodynamic variables, particularly pulmonary capillary wedge pressure as an index of left atrial pressure, during lower body positive and negative pressure. We also examined the correlations between changes in Doppler-derived parameters and those in pulmonary capillary wedge pressure during the procedures.

METHODS

Subjects: We examined 15 men (mean age 55 years, range 36 to 71). Characteristics of these patients are listed in Table I. Twelve patients had coronary artery disease (7 had old myocardial infarction) and 3 had dilated cardiomyopathy of unknown etiology. Patients with clinical evidence of mitral stenosis or aortic regurgitation were excluded. These diagnoses had been confirmed by diagnostic catheterization, including LV contrast cineangiography and coronary arteriography. Mitral regurgitation of a minimal degree (1+) was demonstrated by left ventriculography in 1 patient (no. 14) and by Doppler echocardiography in 4 patients (nos. 5, 11, 12 and 14). No patient had taken β-adrenergic blockers for at least a week before the study. Other drugs such as calcium antagonists and nitrates were stopped on the day of the procedures.

Hemodynamic measurements: Informed consent was obtained from all the subjects and the protocol was

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TABLE I Clinical Characteristics and Changes in Hemodynamic and Doppler Echocardiographic Parameters During Lower Body Positive and Negative Pressure Method

				Pulmonary Capillary Wedge Pressure (mm Hg)						Mean Systemic Arterial Pressure (mm Hg)					Heart Rate (beats/min)					Peak Velocities of LV Diastolic Filling Flow (cm/s) Early (R)					Late (A)				
Pt	Age (yrs)	Diagnosis	LVEF (%)	LBP (mm Hg)	+20	+10	0	−20	−40	+20	+10	0	−20	−40	+20	+10	0	−20	−40	+20	+10	0	−20	−40	+20	+10	0	−20	−40
1	65	CAD	83		12	7	5	3	5	117	109	94	94	89	53	51	56	56	59	38	36	34	34	27	57	49	52	54	51
2	67	CAD	83		20	15	9	6	8	140	125	114	118	118	57	55	56	57	63	53	49	40	29	21	54	49	47	46	37
3	71	CAD	67		7	8	4	3	2	118	113	116	103	101	72	71	73	74	81	27	25	25	23	20	49	45	47	42	35
4	49	CAD	76		12	7	6	5	4	113	111	102	100	100	74	74	77	79	81	36	35	30	26	21	57	46	45	41	39
5	43	CAD	74		14	12	8	7	4	96	95	90	86	83	62	59	60	59	67	52	48	42	38	29	47	42	38	35	32
6	58	OMI (A, Ap)	61		8	6	4	2	3	101	99	93	80	79	76	78	78	82	88	36	32	33	25	19	34	30	32	32	27
7	57	OMI (A, Ap)	42		12	7	6	3	2	110	109	107	102	97	74	72	74	76	79	28	35	33	25	19	55	55	53	42	32
8	67	OMI (A, Ap, I)	42		10	8	5	3	2	124	121	117	116	104	82	75	74	76	83	50	46	45	34	29	33	34	30	29	28
9	36	OMI (A, Ap)	47		19	14	9	6	5	97	95	96	91	91	65	58	57	56	65	24	27	27	22	17	55	56	56	55	56
10	49	OMI (A)	58		19	12	9	4	3	97	93	92	91	92	67	67	67	62	66	56	52	50	41	35	45	44	40	40	35
11	47	OMI (A, Ap)	59		15	8	5	3	2	96	91	89	85	82	59	53	53	52	58	43	37	35	27	24	34	27	24	21	24
12	49	OMI (P)	58		13	11	7	3	3	97	93	85	85	85	68	63	63	62	67	57	44	40	25	25	44	43	38	34	30
13	51	DC	31		29	22	16	10	6	99	93	92	89	72	63	63	62	69	72	34	38	33	21	23	26	23	26	24	13
14	62	DC	26		14	14	12	10	8	103	107	102	109	107	52	54	55	57	61	41	39	27	23	18	26	39	31	35	38
15	49	DC	27		17	17	13	12	9	99	99	98	100	96	75	74	75	78	85	44	44	26	23	22	41	41	36	36	43
Mean	55		56		15	11	8	5	4	107	103	99	97	93	67	64	65	66	72	41	39	35	28	24	44	42	40	38	35
SD	10		19		5	4	3	3	2	13	11	10	11	12	9	9	9	10	10	10	8	7	6	5	11	9	10	9	10
					†	†		†	†	†				†					†	†	*		†	†	*				

* $p < 0.05$, † $p < 0.01$ vs values at LBP of 0 mm Hg.
CAD = coronary artery disease; DC = dilated cardiomyopathy; LBP = lower body pressure; LVEF = left ventricular ejection fraction calculated from LV contrast cineangiograms of the 30° right anterior oblique position; OMI = old myocardial infarction; SD = standard deviation; the localizations of segmental wall motion abnormalities determined from LV cineangiograms are shown in parentheses (A = anterior; Ap = apical; I = inferior; P = posterior).

approved by the Ethical Committee of the Hospital of the University of Tokyo. Right-sided heart catheterization was done percutaneously via the subclavian vein of either side. A 7Fr balloon-tipped thermodilution catheter (Gould Inc.) was advanced into the pulmonary artery and connected to a Statham P50 pressure transducer (Gould Inc.) to measure pulmonary capillary wedge pressure. A 23-gauge polyethylene tube was inserted into the radial or brachial artery percutaneously and connected to another Statham P50 pressure transducer to monitor peripheral arterial pressure. Pressure signals were amplified by a DS-1100 patient monitoring system (Fukuda Denshi, Ltd.) and recorded on a thermal array recorder AU-5001 (Fukuda Denshi, Ltd.) at a paper speed of 50 mm/s.

Doppler and M-mode echocardiographic measurements: A color flow mapping Doppler echocardiograph (SSD-880, Aloka Ltd.) was used. Ultrasonic frequency was 2.5 MHz and pulse repetition rate was 2 kHz. Using the apical approach, we imaged the LV long-axis view. A sample volume was positioned in the center of the mitral anulus in diastole, with reference to 2-dimensional echo images. We tried to maintain the sample volume at the same position throughout the procedures. The detected Doppler signals were analyzed with a spectral analyzer based on fast Fourier transform and recorded on a stripchart recorder (SSZ-95, Aloka Ltd.) at a paper speed of 50 mm/s. The peak velocities of LV early and late diastolic filling flow were calculated from the Doppler shifts determined as the midpoints of the Doppler spectrum and the angle between mitral inflow and the ultrasonic beam.[1,5] Measurements were done by 2 independent observers and averaged values were adopted for statistical analyses.

Protocol: Patients were positioned supinely with the lower half of their bodies below iliac crests sealed in a transparent box made of acrylics. For lower body positive pressure method we sent air into the box, and for lower body negative pressure method we evacuated the box with a vacuum cleaner pump. We controlled an intracavitary pressure of the box (lower body pressure) by changing the power of the pump and monitored this pressure with a sphygmomanometer. We initially increased lower body pressure to +20 mm Hg versus atmospheric pressure, and then decreased it to +10, 0, −20 and −40 mm Hg stepwise, every 3 minutes. We performed hemodynamic and Doppler echocardiographic measurements at the end of each step while the subjects held respiration at end-expiration. All the data points were obtained at the descending phase[14] of lower body positive and negative pressure, where lower body pressure was always altered to a smaller value.

Data analysis: Average values of 5 successive beats were used for the statistical analyses. All values were expressed as mean ± standard deviation. We first attempted 2-way analysis of variance, and then compared the values obtained at lower body pressure of +20, +10, −20, or −40 mm Hg with those obtained at lower body pressure of 0 mm Hg using the paired *t* test with Bonferroni's correction[15] if overall significant difference was found with analysis of variance. Linear correlation analysis was also used. Significance was accepted at the $p < 0.05$ level.

RESULTS

Changes in hemodynamic variables: Changes in hemodynamic variables during lower body positive and negative pressure are listed in Table I. Mean pulmonary capillary wedge pressure increased during lower body positive pressure and decreased during negative pressure significantly, in a fashion parallel to lower body pressure. Mean systemic arterial pressure increased during lower body positive pressure and decreased at lower body pressure of −40 mm Hg. Heart rate was almost unchanged except at lower body pressure of −40 mm Hg (9% increase from the value at lower body pressure of 0 mm Hg).

Changes in Doppler echocardiographic variables: Figure 1 shows changes in LV diastolic filling flow obtained with Doppler echocardiography in 2 representative patients, one with old myocardial infarction and one with dilated cardiomyopathy.

Changes in Doppler echocardiographic variables during the procedures are also listed in Table I. The peak velocity of LV early diastolic filling flow increased during lower body positive pressure and decreased during negative pressure, in an almost parallel fashion with lower body pressure. By contrast, the peak velocity of LV late diastolic filling flow remained unchanged significantly except at lower body pressure of +20 mm Hg.

Correlative relations between parameters of left ventricular diastolic filling flow and pulmonary capillary wedge pressure: A positive correlation was found between changes in the peak velocity of LV early dia-

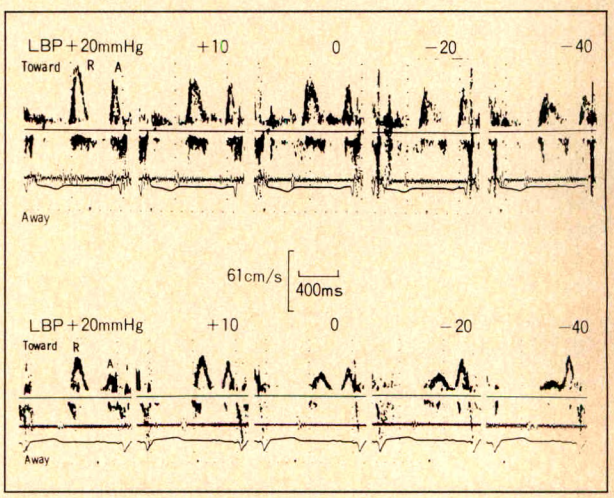


FIGURE 1. Changes in left ventricular (LV) diastolic filling flow obtained with pulsed Doppler echocardiography in a patient (no. 12, Table I) with posterior myocardial infarction (*top*) and a patient (no. 14, Table I) with dilated cardiomyopathy (*bottom*). The peak velocity of LV early diastolic filling flow (R) was changed with lower body pressure (LBP) almost in a parallel fashion during lower body positive and negative pressure method. Changes in the peak velocity of LV late diastolic filling flow (A) were less significant.

stolic filling flow and changes in pulmonary capillary wedge pressure during lower body negative pressure of −20 mm Hg (r = 0.759, p <0.01, Figure 2A). The changes were calculated by subtracting the values at lower body pressure of 0 mm Hg from those at lower body pressure of −20 mm Hg. In contrast, changes in the peak velocity of LV late diastolic filling flow did not correlate significantly with the changes in pulmonary capillary wedge pressure (r = 0.039, not significant, Figure 2B) during this step of lower body negative pressure.

DISCUSSION

In this study, we used lower body positive and negative pressure method to control venous return. This method could change both pulmonary capillary wedge pressure and the peak velocity of LV early diastolic filling flow stepwise in wide ranges. By contrast, only small changes were provoked in mean systemic arterial pressure and heart rate, indicating that only small changes occurred in LV afterload and sympathetic tone.

Other investigators[11,12] have tried to reduce venous return using nitroglycerin while examining patients with Doppler echocardiography. They reported changes in Doppler-derived parameters of LV diastolic filling flow similar to those obtained during lower body negative pressure. Nitroglycerin could be given easily to patients, but could not alter left atrial pressure without affecting other parameters.[11] Furthermore, it was difficult to alter venous return stepwise with this drug.

We obtained LV diastolic filling flow with pulsed Doppler echocardiography, because this method could provide a noninvasive and direct evaluation of flow on a beat-by-beat basis, independently from LV geometry.[1,5,8,11] Other methods such as LV contrast cineangiography and radionuclide angiography were not feasible in this study, where repeated measurements of parameters of diastolic filling were required at short intervals.

LV diastolic filling is a complex process determined by multiple factors.[16] Some clinical studies[4–6] stressed the exclusive importance of the rate of LV relaxation in early diastolic filling dynamics, but other experimental[7,8] and clinical[9,11,12] studies suggested the importance of both left atrial pressure and the rate of relaxation. In the present study, changes in the rate of LV relaxation appeared to be small, because changes in LV afterload and sympathetic tone, which would have affected the rate of relaxation,[17,18] were small during the procedures. Isolated changes in preload are known not to alter the rate of LV relaxation significantly.[19] Therefore, we could demonstrate the close relation between changes in left atrial pressure and the peak velocity of LV early diastolic filling flow especially during lower body negative pressure of −20 mm Hg when mean arterial pressure and heart rate were unchanged.

The peak velocity of LV late diastolic filling flow was less changed than that of early filling in this study. This finding is compatible with the results of the previous clinical studies using nitroglycerin.[11,12] The mechanism accounting for this phenomenon would be complex because LV late diastolic filling flow is determined not only by the factors affecting early diastolic filling, but also by pump function of the left atrium. An interplay between preload and afterload of the left atrium, both of which are in part determined by LV early diastolic filling volume, might be responsible for this finding.

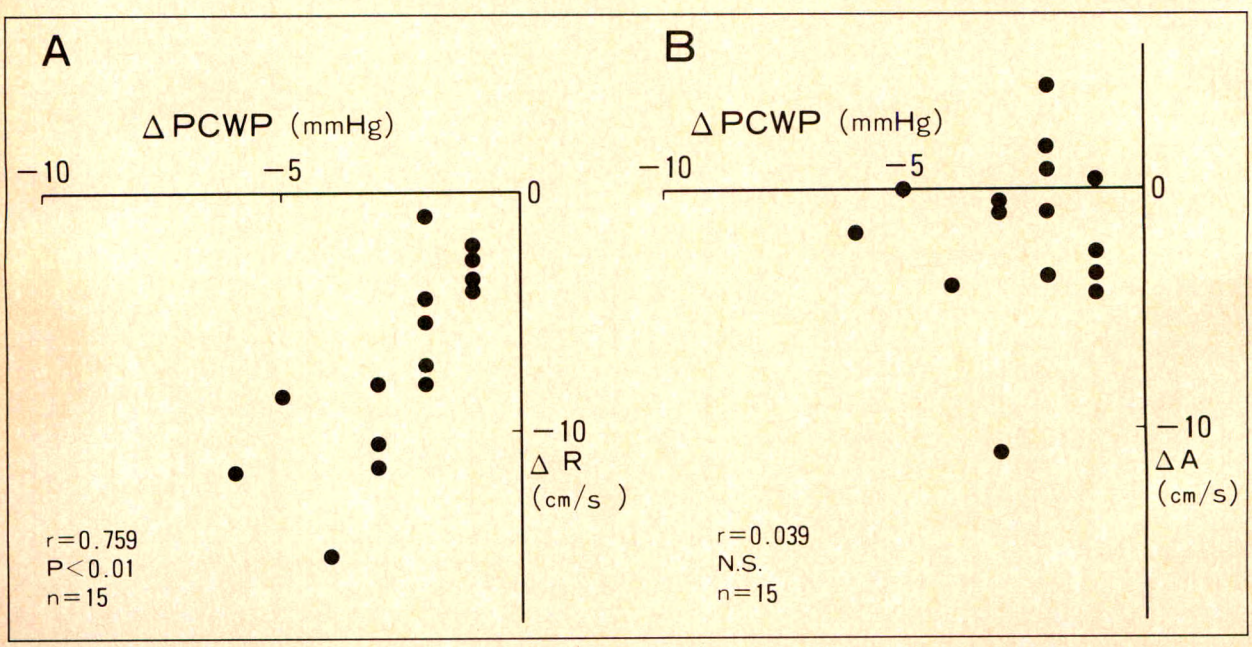


FIGURE 2. ***A*, correlation between changes in the peak velocity of left ventricular (LV) early diastolic filling flow (ΔR) and changes in pulmonary capillary wedge pressure (ΔPCWP). These changes were calculated by subtracting the values obtained at lower body pressure of 0 mm Hg from those at lower body pressure of −20 mm Hg. A positive linear correlation was demonstrated between ΔR and ΔPCWP (r = 0.759, p <0.01). *B*, no significant correlation was found between changes in the peak velocity of LV late diastolic filling flow (ΔA) and ΔPCWP (r = 0.039).**

Some limitations of this study should be considered. We did not measure phasic LV and left atrial pressures because of technical difficulties. Instead, we adopted mean pulmonary capillary wedge pressure as an expression of left atrial pressure. Although this pulmonary capillary wedge pressure represents not only left atrial pressure, but also LV filling pressure partly determined by LV diastolic properties, we assumed that LV diastolic properties were little affected during lower body positive and negative pressure.

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Usefulness of Jogging in Place as an Exercise Test of Enhanced Diagnostic Efficacy

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This study, an extension of a previous one,[1] compares the results of a jogging in place exercise test against the standard Bruce protocol with those of coronary arteriography in a new series of patients. We show that the jogging test, monitored and recorded with a single-channel electrocardiograph, offers superior diagnostic performance to the Bruce protocol monitored and recorded in a 3-channel apparatus.

One-hundred twenty-five new patients underwent coronary arteriography, and also consecutive jogging in place and Bruce protocol treadmill tests. They were 118 men and 7 women, 24 to 73 years old, with a mean (± standard deviation) age of 54 ± 8 years. The reason for performing the exercise tests and the arteriography was definite or suspected coronary artery disease. Sixty of the patients had typical angina pectoris, 16 had atypical (probable) angina, 29 had nonspecific chest complaints and 20 were asymptomatic (all with old myocardial infarction). In 63 patients, there was a history or electrocardiographic evidence of prior myocardial infarction.

The exercise tests were performed either before or after coronary arteriography. In most patients, the time lag between exercise tests and coronary arteriography did not exceed 1 week. The tests were separated by at least 1 hour (to a few days for most); the order was random and they were maximal symptom-limited.

A positive exercise electrocardiogram was defined as either ST-segment depression ≥1 mm measured 80 ms from the J point (in addition to any preexisting degree), or ST-segment elevation ≥1 mm or U-wave inversion. The reasons for stopping either test were: chest pain of progressive severity, significant (≥2 mm) ST-segment depression, achievement of the maximum age-predicted heart rate, runs of ventricular tachycardia, excessive (>250 mm Hg) systolic blood pressure or hypotension (<90 mm Hg) or inability to continue the test. For the details concerning the technical performance of the 2 tests, see our previous report.[1]

The criterion of significant coronary artery stenosis was ≥70% narrowing in diameter; it was ≥50% for the left main stem. Of the 125 patients, 50 had 1-vessel disease, 41 had 2-vessel disease (including 3 involving the left main), 11 had 3-vessel disease, 1 had 4-vessel disease and 22 had either normal coronaries (15) or nonsignificant stenoses (7).

Sensitivity is the percentage of patients with positive exercise electrocardiograms and coronary artery disease (true positives) divided by the total number of patients with coronary artery disease. Specificity is the percentage of the patients with normal exercise electrocardiograms without coronary artery disease (true negatives) divided by the total number of patients without coronary artery disease. Correct classification rate of the test is the sum of true positives and true negatives, divided by the total number of patients studied. The statistical tests were chi-square for comparisons of proportions of unpaired observations, paired t test for means of continuous variables and the McNemar test for the discordant results of the paired observations.[2]

TABLE I Results of Exercise Tests in Patients with Coronary Artery Disease

		Bruce Treadmill Protocol		
		Positive	Negative	Total
Jogging in place	Positive	49	17	66
	Negative	4	33	37
Total		53	50	103

TABLE II Results of Exercise Tests in Patients Without Coronary Artery Disease

		Bruce Treadmill Protocol		
		Positive	Negative	Total
Jogging in place	Positive	3	0	3
	Negative	4	15	19
Total		7	15	22

Table I lists the results of the 2 tests in patients with coronary artery disease; it is evident that there is concordance in 80% (82 of 103) and discordance in 20% (21 of 103). These latter patients were analyzed as positive only by jogging test (17) and positive only by Bruce test (4). This difference is statistically significant (McNemar's u = 2.83 with corresponding p = 0.005 for 2-tailed comparison)—implying a significantly higher sensitivity for the jogging test versus the Bruce test (64 [66 of 103] vs 51% [53 of 103]). Within the context of patients with coronary artery disease, both the peak exercise heart rate (156 ± 22 vs 142 ± 23 beats/min, p <0.0001) and the peak exercise double product (28,351 ± 6,451 vs 24,513 ± 5,681 beats × mm Hg/min, p <0.0001) were significantly higher with the jogging test for the same tested persons. The mean ± standard deviation number of significantly narrowed coronary arteries did not significantly differ between concordant positive tests (1.7 ± 0.7) and concordant negative tests (1.6 ± 0.7). This also applied to patients with only positive Bruce tests (1.7 ± 0.9) or only positive jogging tests (1.5 ± 0.5). In contrast, the proportion of patients with typical angina was significantly higher among concordant positive tests (71% [35 of 49]) than among concordant negative tests (24% [8 of 33], p <0.01). Also all 4 patients with left main disease had concordant positive test results.

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Table II lists the results of the 2 tests in patients free of significant coronary artery disease. It is evident that there is concordance in 82% (18 of 22) and discordance in 18% (4 of 22) where only the Bruce test gave a positive result. This is statistically significant (McNemar's u = 2.0 with corresponding p = 0.046 for 2-tailed comparison)—implying a significantly higher specificity for the jogging test versus the Bruce test (86 [19 of 22] vs 68% [15 of 22]).

Even among patients without significant coronary artery disease, the jogging test had significantly higher values for both peak exercise heart rate (170 ± 15 vs 155 ± 19 beats/min, p <0.005) and peak exercise double product (33,193 ± 5,860 vs 27,937 ± 4,352 beats × mm Hg/min, p <0.005).

The sum of the respective patients summarized in Tables I and II gives the number of the correctly classified patients: 68 (55%) by the Bruce and 85 patients (68%) by the jogging exercise test. Of these patients the 2 tests were in agreement in 64. In 4 patients the Bruce protocol was the only correct test, whereas jogging in place was the only correct test in 21. This 21 versus 4 difference, in favor of the jogging test, was highly significant with the McNemar's test (u = 3.4 with corresponding p = 0.00068 for 2-tailed comparison).

In the present report, the comparison of the 2 exercise tests with the coronary arteriographic findings shows that the higher yield of the positive results by the jogging test corresponds to statistically significant higher sensitivity (64 vs 51%), higher specificity (86 vs 68%) and higher correct classification rate (68 vs 55%).

The superior diagnostic performance of the jogging test compared to the standard Bruce test parallels the higher indirect markers of myocardial oxygen consumption: peak heart rate and peak exercise double product achieved by the first test. Thus, the jogging in place exercise test combines a higher diagnostic efficacy with simplicity of implementation and application and a shorter performance time.[1] The better tolerance of this test applies to the entire spectrum—even older persons of both sexes—of persons undergoing an exercise test.

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Effect of Cigarette Smoke on Sinus Node Automaticity

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Neither ambulatory monitoring nor laboratory evaluation of humans or animals has revealed a predictable pattern of change in heart rate related to smoking.[1–3] Disparate observations may be related to the complex autonomic effects of smoke components combined with physiologic responses to the actual inhalation of smoke. This study was conducted to determine the direct effect of cigarette smoking on sinus node automaticity by measuring sinus cycle length changes in subjects who smoked cigarettes after the sinus node was chemically denervated using atropine and propranolol.

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Sixteen smokers volunteered for the study, which was approved by the Cooper Hospital/University Medical Center Institutional Review Committee. Mean patient age was 55 years (range 26 to 78). Fourteen patients were men and 2 were women. Indication for electrophysiology study was nonsustained ventricular tachycardia (VT) in 4 patients, sustained VT in 1 patient, supraventricular tachycardia in 1 patient, syncope in 6 patients, palpita-

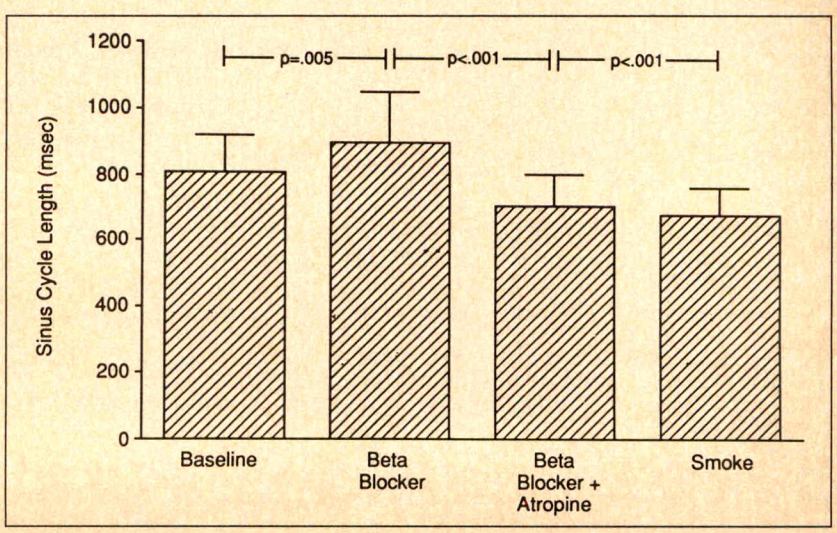


FIGURE 1. Effect of β blockade, parasympathetic blockade after β blockade (β blocker + atropine) and cigarette smoking on sinus cycle length in 16 patients without known sinus node dysfunction.

tions in 3 patients and conduction system disease in 1 patient. Three patients had coronary artery disease, 6 had nonischemic dilated cardiomyopathy, 1 had mitral valve prolapse and 6 patients had no known heart disease. No patient had clinical evidence of sinus node dysfunction. The average corrected maximal sinus node recovery time was 331 ± 146 ms.

After providing informed consent, 15 patients underwent electrophysiologic study alone and 1 underwent cardiac catheterization followed by electrophysiologic testing. In each patient, a 6Fr quadripolar pacing catheter was placed in the high right atrium near the sinus node. Intracardiac electrograms as well as surface leads I, aVF and V_1 were displayed on a Siemens 16-channel oscilloscope and recorded on a Mingograf 16-channel ink-jet recorder. Mean sinus cycle length was determined from the permanent recording of the high right atrial electrogram, averaging at least 5 consecutive intervals.

Patients abstained from smoking for at least 12 hours before the study. Following completion of the baseline electrophysiologic study the patients were allowed to rest for 5 minutes and baseline sinus cycle length was determined. Fourteen patients were then given propranolol intravenously in 1- to 2-mg boluses repeated every minute until heart rate was reduced by 20% or a maximum dose of 0.15 mg/kg of body weight was administered. Patients given intravenous propranolol received an average dose of 11 mg (range 8 to 15). One patient was given 10 mg of intravenous metoprolol. Sinus cycle length was again recorded. One patient taking oral propranolol, 200 mg 4 times daily, was not given intravenous β blocker. Atropine was administered intravenously in a dose of 1 to 2 mg depending on body weight and heart rate after the first mg. Intrinsic heart rate was determined.

Each patient smoked 2 filtered cigarettes over a 5-minute period. They were instructed to smoke continuously and to inhale the smoke. The shortest sinus cycle length recorded within 5 minutes after cessation of smoking was used for analysis. It has been shown that the maximal change in heart rate after smoking occurs within 5 to 10 minutes.[3]

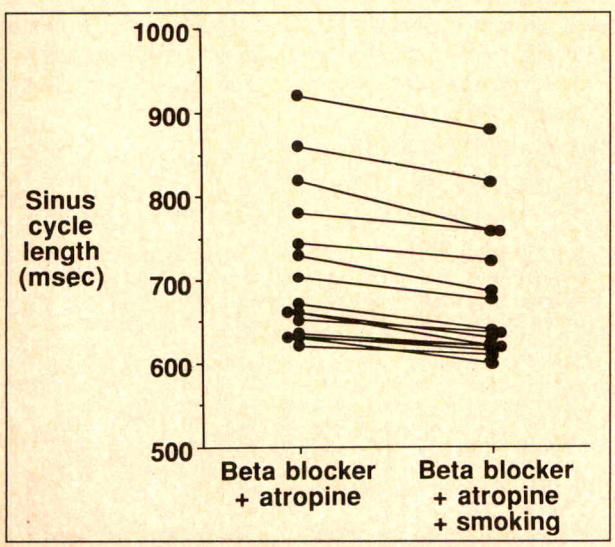


FIGURE 2. Cigarette smoking increased sinus cycle in all patients compared to intrinsic heart rate (heart rate after β blockers and atropine).

As shown in Figure 1, β blockade produced a significant prolongation in sinus cycle length compared to the sinus cycle length at rest (808 ± 112 to 900 ± 152 ms, $p < 0.005$). All patients had an increase in sinus cycle length after β-blocker administration. Removal of vagal influences with atropine produced a significant shortening in sinus cycle length (900 ± 152 to 709 ± 92 ms, $p < 0.001$). Compared to β blockade alone, the sinus cycle length shortened after atropine in all patients. Compared to baseline sinus rhythm, the intrinsic sinus cycle length was shorter in all patients except one. Thus, after chemical denervation of the sinus node with β blockers and atropine, the mean sinus cycle length was significantly shorter than at baseline ($p < 0.005$).

Smoking produced an acceleration of sinus node automaticity in all cases after the sinus node had been chemically denervated (Figure 2). The average sinus cycle length shortened from 709 ± 92 ms before smoking to 681 ± 84 ms after smoking ($p < 0.001$). As shown in Figure 3A, there was no correlation between the degree of smoking-induced cycle length change and the resting sinus cycle length ($r = -0.2$). Thus, with intact sympathetic and parasympathetic circuits, the change in sinus cycle length produced by smoking could not be predicted by the resting sinus cycle length. However, there was a significant inverse relation between the chemically denervated sinus rate and the degree of smoking-induced sinus cycle length acceleration ($r = -0.6$, Figure 3B) suggesting that after chemical denervation, those sinus node cells with a longer phase 4 depolarization (i.e., longer sinus cycle length) were more sensitive to the direct effects of cigarette smoke.

In the chemically denervated human sinus node, we found the inhalation of cigarette smoke to increase heart rate. In isolated atrial tissue, nicotine produces a biphasic response in automaticity. There is an initial rate slowing due to direct parasympathetic ganglionic stimulation followed by rate acceleration due to release of epinephrine and norepinephrine from intracardiac stores.[4] Thus, nicotine has both direct cholinergic and adrenergic effects that are independent of an intact autonomic nervous system.

The effects of smoking are more complex than those of nicotine alone, however, insofar as both sympathetic and parasympathetic nervous system activities are stimulated by smoking. Increased systemic adrenergic tone, as demonstrated by increasing levels of plasma epinephrine and norepinephrine, occurs during smoking.[5] Also, studies of smoke inhalation have revealed reflex bradycardia mediated by direct stimulation of pulmonary receptors by smoke, which increases vagal activity.[6] In this study, the smoking-induced increase in heart rate is a direct effect of cigarette smoke since β-sympathetic neural circuits were blocked with propranolol and reflex parasympathetic arcs were blocked with atropine. This study did not compare the effects of nicotine alone to those changes produced by cigarette smoke with its many components.

While cigarette smoke may have produced a direct effect on the sinus node by increasing automaticity, other

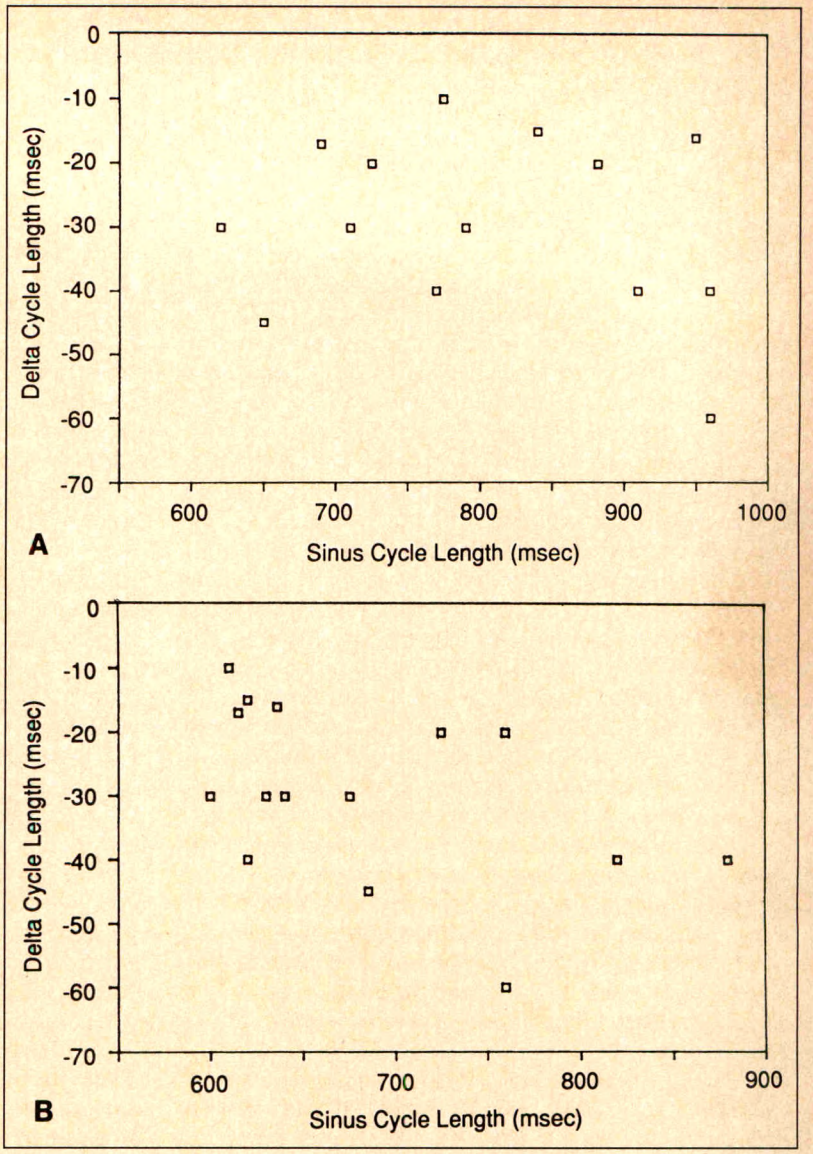


FIGURE 3. ***A,*** **comparison of the sinus cycle length before administration of propranolol and atropine (X axis) to the change in sinus cycle length produced by smoking (Y axis). Correlation coefficient is −0.2.** ***B,*** **comparison of the sinus cycle length after the administration of propranolol and atropine (X axis) to the change in sinus cycle length produced by smoking (Y axis). Correlation coefficient is −0.6.**

possible explanations exist. Smoking may have enhanced automaticity in areas of the atria separate from the sinus node. It has been shown that "sinus" beats do not always originate in the area of the sinus node.[7] The term "atrial pacemaker complex" is used to describe rhythms that appear to be sinus in origin but during atrial mapping studies have been found to originate in other areas of the atria. These atrial pacemaker complexes may be sensitive to endogenous stimulation, and it is possible that the increased heart rate observed after smoking was due to a shift in the atrial pacemaker site. Subtle shifts within the sinus node itself may actually account for the normal sinus acceleration and deceleration. Although the atrial activation sequence assessed by P-wave morphology and 1 intracardiac recording site did not appear to change, detailed atrial mapping was not performed; therefore, minor shifts in the atrial pacemaker site cannot be excluded.

In conclusion, after chemical denervation of the sinus node with β blockers and atropine, exposure to cigarette smoke produces a statistically significant shortening of the sinus cycle length. This may be due to the direct effect of cigarette smoke on the sinus node or to its effect on other atrial pacemakers with a shift of the atrial pacemaker complex.

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Pulmonary Venous Flow Determined by Doppler Echocardiography in Mitral Stenosis

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Recent studies have shown that pulmonary venous flow is normally biphasic. Both phases depend on changes in left atrial pressure that occur during the cardiac cycle.[1-3] The first phase corresponds to ventricular systole and is dependent on ventricular contraction and on a timed relaxation of the left atrium. The second phase occurs during diastole and follows the reduction in atrial pressure during the rapid transmitral flow and ventricular filling. In mitral stenosis (MS), flow rate across the mitral valve is reduced, as is the rate of left atrial pressure decay and left ventricular pressure rise.[4] These changes in left atrial hemodynamics may affect left atrial filling from the pulmonary veins. Moreover, many patients with MS have atrial fibrillation. This arrythmia results in a reduced systolic (J) phase of pulmonary venous flow.[1,5] The present study examines the pattern of pulmonary venous flow velocity in patients with MS.

Fifteen patients (10 women, 5 men) with MS were included in the study. Their ages ranged from 30 to 64 years. Their mean mitral valve area obtained by echocardiography was 1.4 ± 0.8 cm² (range 0.6 to 2.4). Eleven patients had mild to moderate MS and were all in sinus rhythm and had normal left ventricular dimensions and function. Four patients had severe MS, 2 of whom were in sinus rhythm and 2 were in atrial fibrillation. The mitral valve area of these 4 patients was 0.6, 0.9, 0.9 and 1.0 cm², respectively. All 4 underwent cardiac catheterization and mitral valve area assessed invasively and noninvasively was well correlated. The pulmonary venous flow velocity and mitral flow velocity data obtained in these patients were compared to data from normal volunteers previously published.[1,6] All patients were in stable clinical condition. The patients in atrial fibrillation were treated with diuretics, digitalis and anticoagulants.

Echocardiography (M-mode and 2-dimensional) and pulsed Doppler echocardiographic studies of mitral and pulmonary venous flow velocity were performed. An Electronics for Medicine/Honeywell Ultraimager was used for both imaging and Doppler flow velocity studies. Mitral flow velocity and pulmonary venous flow velocity were recorded from the apical 4-chamber view. To obtain mitral flow velocity in the pulsed Doppler mode, the sampling volume was positioned between the tips of the mitral leaflets in the left ventricle, whereas to obtain pulmonary venous flow velocity, the transducer had to be rotated, sometimes slightly, so that the orifices of the pulmonary veins into the left atrium were well visualized and the sampling volume was positioned in place. Mitral flow velocity was also obtained with an independent continuous wave Doppler probe using a Vingmed instrument. Echocardiographic and Doppler flow studies were recorded on a black and white hard copy recorder. In patients with sinus rhythm and mild to moderate MS the temporal relation between the phases of mitral flow velocity, pulmonary venous flow velocity and mitral valve motion were analyzed by matching records of similar RR intervals. Five cycles were analyzed for each data point and all the temporal measurements were referenced to the beginning of the QRS complex. A complete description of the analysis method has been provided previously.[1,2] In 2 patients with severe MS and sinus

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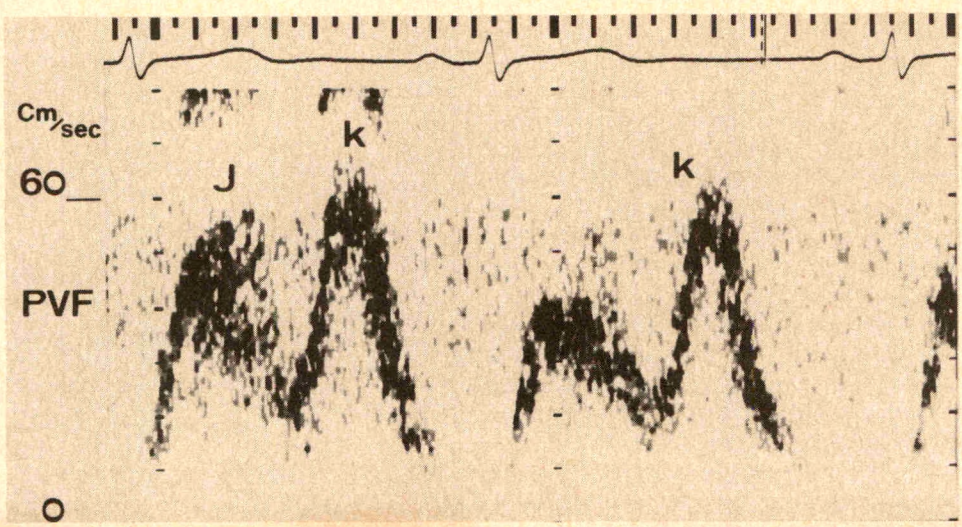


FIGURE 1. Normal pattern of pulmonary venous flow (PVF) velocity. The J phase occurs during systole and the K phase during diastole.

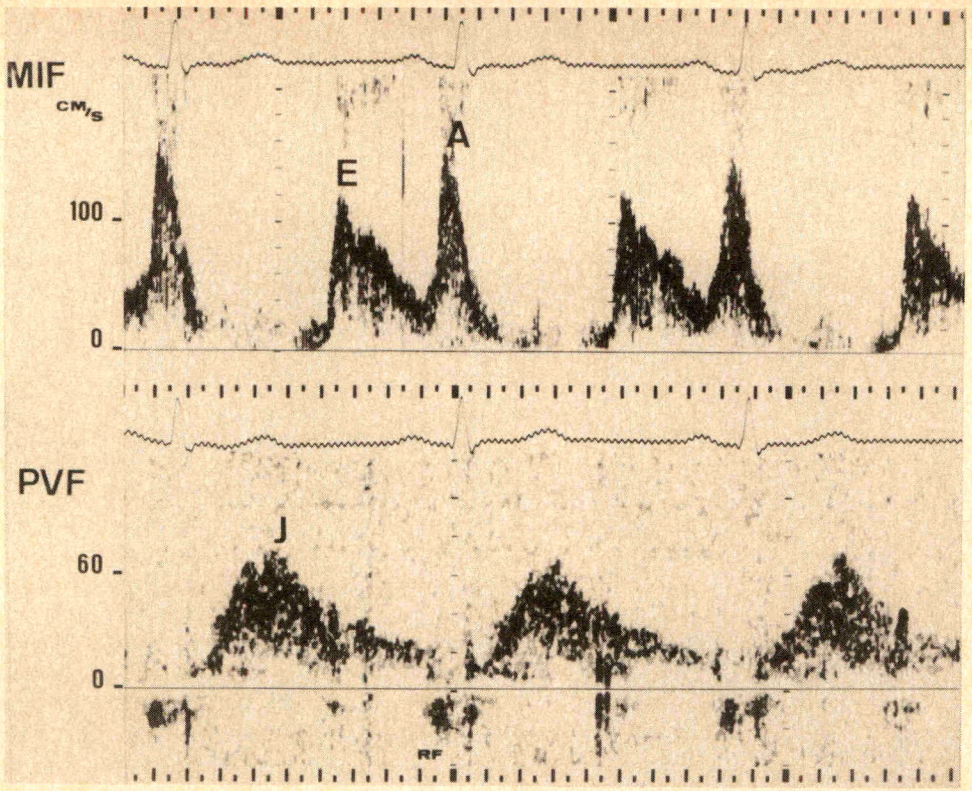


FIGURE 2. Mitral flow velocity (MIF) and pulmonary venous flow (PVF) velocity in a patient with very mild mitral stenosis (mitral valve area 2.2 cm^2). Note that the diastolic phase of pulmonary venous flow is reduced and continuous throughout the end of diastole with retrograde flow during atrial contraction.

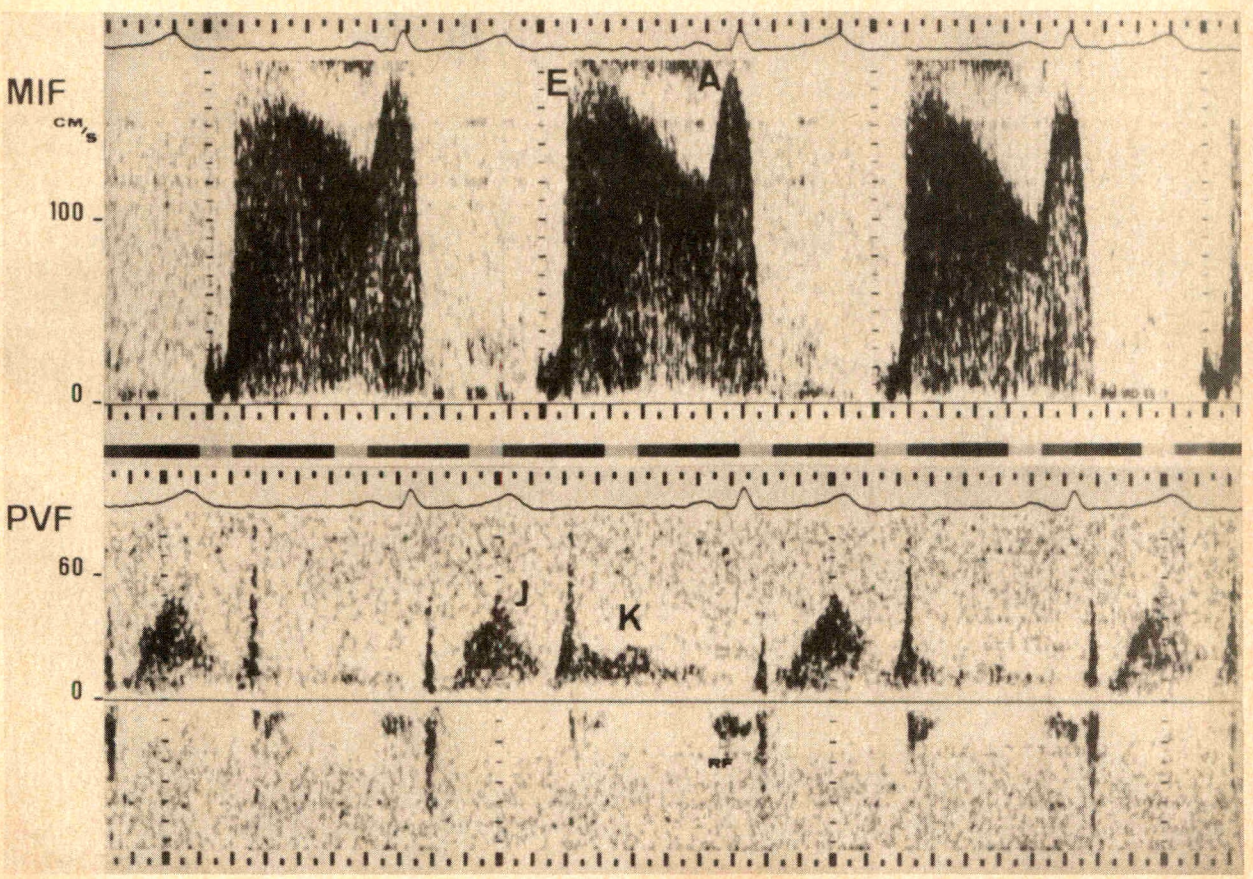


FIGURE 3. Pulmonary venous flow velocity in a patient with significant mitral stenosis (1.1 cm^2). Notice the reduced flow velocity during the diastolic K phase. Notice the regurgitant flow (RF) during atrial contraction. Abbreviations as in Figure 2.

TABLE I Pulmonary Venous Flow and Mitral Flow Velocity Measurements in Mild to Moderate Mitral Stenosis (n = 11)

	RR (ms)	Q→BJ (ms)	Q→J (ms)	Q→K (ms)	Q→KE (ms)	J (cm/s)	K (cm/s)		RR (ms)	Q→D (ms)	Q→E (ms)	Q→A (ms)	Q→C (ms)	E (cm/s)	A (cm/s)
PVF	855 ± 190	115 ± 26	263 ± 43	619 ± 104	818 ± 160	49 ± 15	30 ± 14	MVF	844 ± 199	459 ± 69	523 ± 75	860 ± 181	935 ± 190	152 ± 18	146 ± 27
NV*						45 ± 10	53 ± 15	NV*							
NV†						48 ± 8	49 ± 11							†79 ± 21	45 ± 16

A = peak velocity of atrial contribution; E = peak velocity of rapid filling wave; J = peak velocity of first phase of PVF; K = highest velocity of diastolic phase of PVF; MVF = mitral flow velocity; PVF = pulmonary venous flow velocity; Q→A = peak atrial contribution; Q → BJ = duration from the beginning of the Q wave on the electrocardiogram to the onset of the J phase of pulmonary venous flow; Q→C = cessation of mitral flow; Q→D = onset of mitral flow; Q→E = peak of rapid filling wave; Q→J = peak of J phase; Q→K = peak of K phase; Q→KE = end of K phase.

* NV = normal values for J and K.[1]

† Normal values.[2]

rhythm who underwent cardiac catheterization, the echo Doppler studies were performed immediately before the hemodynamic study. Doppler flow velocity tracings were matched to hemodynamics data by superimposing Figures 4 and 5 with reference to the R wave of the electrocardiogram.

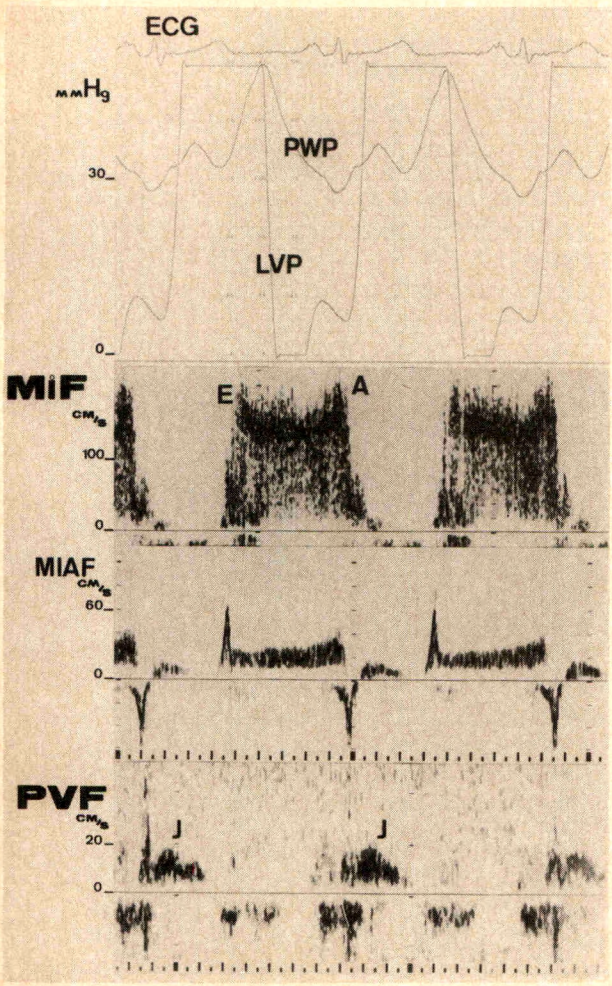


FIGURE 4. Superimposed figure of pulmonary venous flow velocity, transmitral flow, left ventricular pressure (LVP) and pulmonary capillary wedge pressure (PWP) in a patient with severe mitral stenosis. Notice that the mean and peak pulmonary capillary wedge pressure during systole is lower than during diastole. Pulmonary venous flow is detected only in systole (J). The small time delay in pulmonary capillary wedge pressure recording should be attributed to the characteristics of the fluid filled catheter transducer system. MIAF = flow at the mitral anulus. Other abbreviations as in Figure 2.

As previously described in normal subjects and as shown in Figure 1 and Table I, pulmonary venous flow velocity is biphasic with a peak velocity of the systolic J phase equal to or smaller than the peak velocity of the K phase. This pattern changes in MS. In 11 patients with mild to moderate MS and normal left ventricular dimensions and function, the first phase of pulmonary venous flow (J) peaked early during ventricular systole and reached a peak velocity of 49 ± 15 cm/s. The diastolic (K) phase of flow was continuous throughout the end of diastole, with a reduced peak flow velocity (30 ± 14 cm/s, Figures 2 and 3). There was no statistically significant correlation between mitral valve area and peak velocity of the J or K phase. The peak of the diastolic K phase of pulmonary venous flow in patients with mild to moderate MS (Table I) occurred significantly later than the peak of the rapid ventricular filling phase (E wave) of mitral flow (619 ± 104 vs 523 ± 75 ms, $p < 0.01$).

In patients with moderate MS marked retrograde flow into the pulmonary veins was observed during atrial contraction. In the patients with severe MS who were in sinus rhythm, the diastolic K phase could not be detected. The systolic phase was the main left atrial filling phase from the pulmonary veins. A marked retrograde flow during atrial contraction was detected in these patients. Figure 4 shows superimposed left ventricular and pulmonary capillary wedge pressures, as well as mitral and pulmonary venous flow velocity tracings, in a patient with severe MS who was in sinus rhythm. Only 1 phase of pulmonary venous flow velocity was detected during ventricular systole (J phase), which corresponded in time to the a-c wave and the x descent of the pulmonary wedge pressure. During early diastole (y descent) left atrial inflow from the pulmonary veins could not be detected by Doppler. Peak and mean pulmonary capillary wedge pressure during systole was lower than during diastole. Conversely, in the patients with severe MS and atrial fibrillation pulmonary venous flow showed 1 major phase during the diastolic K phase, and the systolic phase was markedly reduced (Figure 5).

All phases of left ventricular filling are disturbed in patients with mitral stenosis. In the normal heart blood flow accelerates rapidly in early diastole and then decelerates due to a decreasing atrioventricular pressure gradient. This early phase of mitral flow correlates in time to the y descent in left atrial pressure, and to the onset of the K phase of pulmonary venous flow. In patients with MS, the rates of atrioventricular pressure gradient decay and

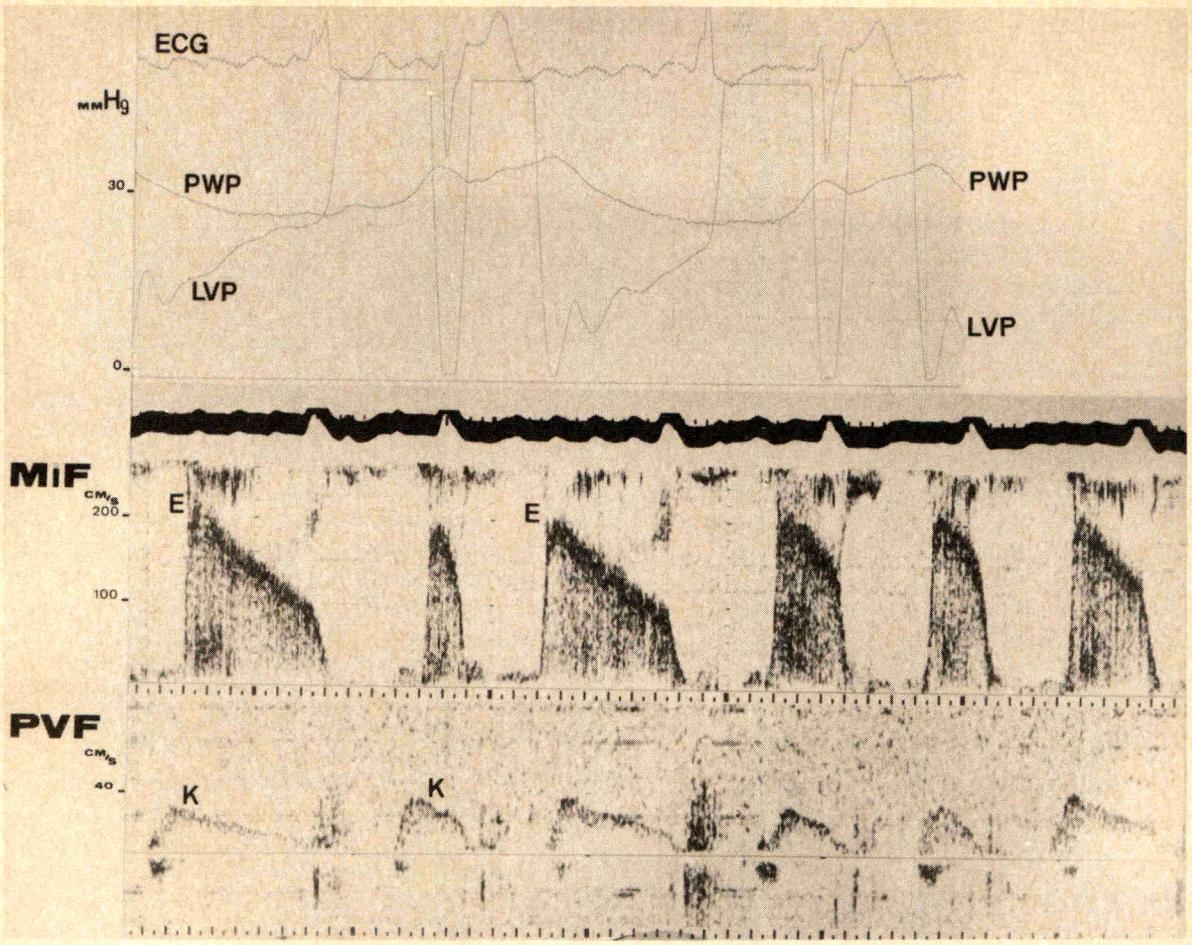


FIGURE 5. Superimposed figure of pulmonary venous flow velocity, transmitral flow velocity, left ventricular and pulmonary capillary wedge pressure in a patient with severe mitral stenosis and atrial fibrillation. The tracings were not simultaneously obtained so that alignment of the electrocardiogram is not exact. Notice that pulmonary venous flow is detected only in diastole (K). Abbreviations as in Figures 2 and 4.

flow deceleration are markedly reduced resulting in increased left atrial pressures throughout diastole. These hemodynamic changes are manifested by a loss of the phasic nature of the diastolic K phase of pulmonary venous flow in MS, which takes a continuous low flow shape in mild to moderate stenosis and is almost undetectable in severe cases. Interestingly, in both patients with severe MS who underwent cardiac catheterization, mean and peak pulmonary capillary wedge pressure was lower during systole than during diastole (Figure 4).

These findings emphasize the importance of left ventricular systolic function in reducing left atrial pressure and augmenting left atrial filling from the pulmonary veins. Both timed atrial relaxation and descent of the mitral anular ring during ventricular systole are important determinants of left atrial filling from the pulmonary veins.[1,5,6] Loss of effective atrial function such as in patients with atrial fibrillation or sinoatrial block results in marked diminution of the J phase and a relative increase in the diastolic K phase of pulmonary venous flow.

In MS, the derangement in atrial myocardium may determine the hemodynamic role of the atrial contraction and may establish the milieu necessary for atrial fibrillation.[7] This arrythmia was recently shown to play a role in determining left atrial size in MS.[8] Thus, it may affect left atrial compliance and contribute to changes in left atrial filling pattern from the pulmonary veins. In patients with mitral stenosis and atrial fibrillation the J phase is markedly reduced due to loss of timed atrial function. The K phase is the main left atrial filling phase and is prolonged (Figure 5) due to the gradual decay of atrioventricular pressure gradient over the stenotic mitral valve.

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Follow-Up After Percutaneous Balloon Valvoplasty for Noncalcific Aortic Stenosis

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This study evaluates the follow-up data from the first 25 patients with noncalcific aortic stenosis who underwent percutaneous balloon aortic valvuloplasty (PBAV) at our center between September 1986 and December 1988.

There were 19 male and 6 female patients, aged 12 ± 9 years (range 1 to 36); 18 were younger than 18 years. All had isolated noncalcific aortic stenosis on clinical and Doppler echocardiographic evaluation, with a Doppler peak systolic gradient >50 mm Hg, and congenitally bicuspid valves. Eleven of these patients (44%) were in New York Heart Association class I, 10 (40%) in class II, 3 (12%) in class III and 1 (4%) was in class IV (Figure 1). Informed consent was obtained from adult patients or the children's parents before PBAV. PBAV was performed in all the patients using a technique already reported.[1] Results in the first 5 patients have previously been reported.[2] Aortic root angiography was performed before and after PBAV, and the degree of aortic regurgitation was graded on a scale of 1 to 4.[3] The aortic valve area was calculated before and after PBAV by the Gorlin equation, and cardiac output was measured by the Fick principle. PBAV was performed with a single balloon in 23 and double balloons in 2 patients. The balloon:aortic anulus ratio, which was measured from angiograms, was 90 ± 8% (range 77 to 100). Statistical analysis was performed using the Student's t test and the level of statistical significance was considered to be p <0.05.

The peak to peak systolic gradient before PBAV was 112 ± 35 mm Hg; it decreased to 44 ± 21 mm Hg (p <0.001) immediately after the procedure. The aortic valve area (n = 20) increased from 0.3 ± 0.07 to 0.69 ± 0.2 cm^2/m^2 (p <0.01). In 1 patient, the balloon catheter was withdrawn with great difficulty after inflation, and the gradient was unchanged. However, the Doppler peak systolic gradient 24 hours later was 50 mm Hg, and has remained so over 6 months, suggesting transient dynamic outflow obstruction. Aortic root angiography before the procedure (n = 24) showed that aortic regurgitation was absent in 14 patients, and was grade 1 in 10 (Figure 2). Immediately after PBAV it was absent in 5, grade 1 in 13 and grade 2 in 6. There were no deaths. Ventricular fibrillation occurred in 2 patients. One patient had prolonged bleeding from the puncture site, and 5 had transient pulse loss. The pulse normalized within 48 hours of heparin infusion in 4 patients, and after intravenous streptokinase in the fifth.

Patients have been followed up for 11 ± 7 months (range 1 to 26). At short-term follow-up (≤6 months) 23 (92%) were asymptomatic (Figure 1). Persistent symptoms were seen in 2 patients. An infant who was in persistent cardiac failure after an unsuccessful PBAV underwent surgical valvotomy. After surgery the peak systolic gradient of 100 mm Hg was reduced to 70 mm Hg as assessed by Doppler. Another patient with a partially successful PBAV (Figure 1) had persistent shortness of breath, and became asymptomatic after a successful re-

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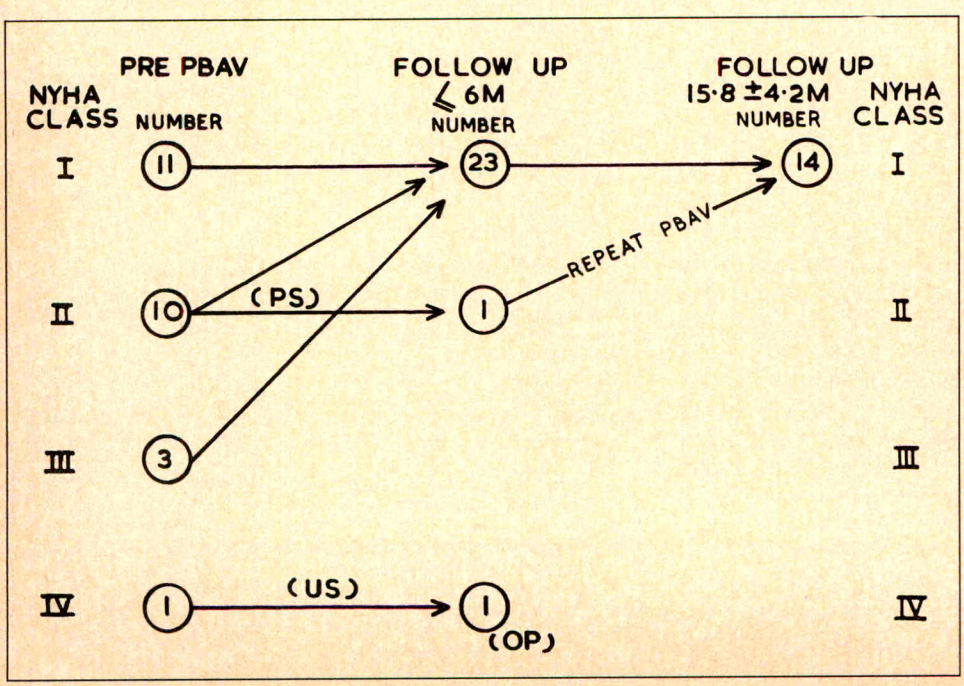


FIGURE 1. Symptomatic status of patients before percutaneous balloon aortic valvuloplasty (PBAV) and on follow-up. Persistent symptoms were seen after a partially successful (PS) or unsuccessful (US) procedure. OP = operated.

peat PBAV. Fourteen of these patients who have been followed up for 15.8 ± 4 months remained in New York Heart Association class I. Repeat catheterization was performed in 13 patients at 11 ± 4 months. Peak systolic gradient immediately after PBAV was 40.0 ± 17.5 mm Hg in these 13 patients and on follow-up it was 45.0 ± 30.0 mm Hg (difference not significant). The aortic valve area (n = 10) was 0.76 ± 0.23 cm^2/m^2 immediately after PBAV and 0.71 ± 0.23 cm^2/m^2 (difference not significant) at follow-up.

Restenosis, defined as >50% loss of initial gain, was seen in 3 patients. In 1 patient it was related to inadequate relief on dilatation with a balloon:anulus ratio of 85%. Repeat catheterization for persistent symptoms 5 months later revealed restenosis, which was successfully treated by dilation with a larger balloon (balloon:anulus ratio of 95%). Asymptomatic restenosis occurred in 2 others despite balloon:anulus ratios of 99 and 91% and thin pliant bicuspid valves on 2-dimensional echocardiography. The angiographic grade of aortic regurgitation (Figure 2) on follow up (n = 12) showed an increase to grade 3 in 2 patients, while in the other it was ≤ grade 2. The grade 3 aortic regurgitation was well tolerated: patients were asymptomatic, with normal left ventricular function on echocardiography. In one of these patients it was related to partial avulsion of the left aortic cusp with a reduction of the gradient from 28 mm Hg immediately after PBAV to 0 mm Hg on repeat catheterization.

In 10 patients who have not had repeat catheterization, the Doppler peak systolic gradient of 106 ± 28 mm Hg was reduced to 59 ± 26 mm Hg (p <0.001) immediately after the procedure, and was unchanged (54 ± 23.0 mm Hg) at 9 ± 7 months of follow up. The reliability of Doppler estimation of the peak systolic gradient has been validated in our laboratory,[4] with good correlation (r = 0.92 p <0.001) with catheterization peak to peak systolic gradient and no significant under- or overestimation. The Doppler grading of aortic regurgitation before PBAV in 9 of these patients showed no aortic regurgitation in 7, and grade 1 in 2. Immediately after PBAV it was absent in 3, grade 1 in 2 and grade 2 in 4. At follow-up there was a decrease by 1 grade in 3 patients, from grade 2 to 1 in 2, and grade 1 to 0 in another. No patient had an increase in severity.

There is limited information on the follow-up of patients who undergo PBAV for noncalcific aortic stenosis.[1,5–8] Most of our patients (92%) were asymptomatic at short-term follow-up; symptom-free status was also maintained in all those who were followed up for 15 months. Persistent symptoms were related to inadequate relief and restenosis. Restenosis after PBAV for noncalcific aortic stenosis has not been reported earlier.[1,5–8] We encountered it in 3 patients. In 1 patient with persistent symptoms repeat successful PBAV was carried out. Asymptomatic restenosis was seen in 2 patients with gradients of 60 and 50 mm Hg; the former has been recommended for repeat PBAV and the latter for medical follow-up. A late increase in the severity of aortic regurgitation to grade 3 (moderate), which occurred in 2 of our cases, is another area of concern. While both of these patients are asymptomatic with normal left ventricular size and function, 1 patient with a similar problem reported by Sholler et al[8] required aortic valve replacement.

In all our patients with inadequate relief, we had used single balloons, and did not exceed a balloon:anulus ratio of 100% in view of experimental[7] and perioperative evidence[9] that overlarge balloons can result in severe aortic regurgitation. Would use of double balloons have reduced the gradient further? Since we used double balloons in only 2 patients, a meaningful comparison is not possible. While Sholler et al[8] did not find the results of the double balloon technique to be superior to single balloons, Beekman et al[10] have reported significantly superior results with the double balloon technique. Hence, although valve morphology is probably the most important determinant of the results of PBAV for noncalcific aortic stenosis,[8]

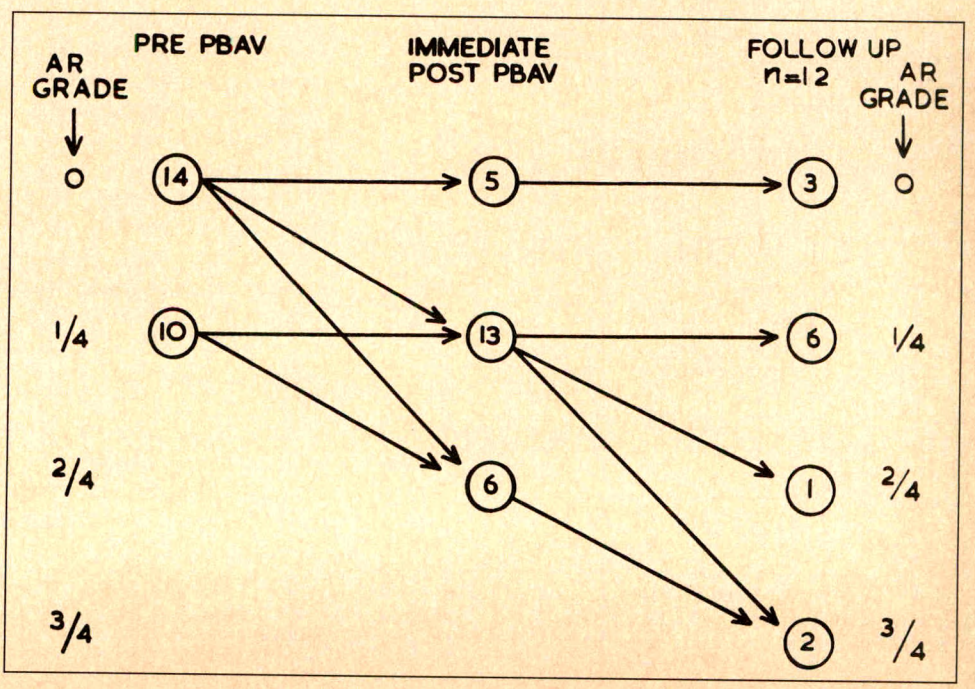


FIGURE 2. Angiographic grades of aortic regurgitation (AR). On follow-up catheterization 2 patients had an increase to grade 3. PBAV = percutaneous balloon aortic valvuloplasty.

technical considerations are not yet free of controversy. Repeat PBAV with double balloons has been recommended to all our patients with significant residual gradients.

The hemodynamic results of PBAV, the sustained symptomatic and hemodynamic benefit in the first 18 months of follow-up, the lack of mortality, the short hospitalization, the uncommon occurrence of restenosis and the absence of severe aortic regurgitation requiring aortic valve replacement are all strong reasons for considering PBAV as the treatment of choice for noncalcific aortic stenosis, especially in children.

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Do Changes in Fraction of Inspired Oxygen Affect Pulmonary Artery Acceleration Time?

Julie H. Ernst, MD, and Stanley J. Goldberg, MD

Pulmonary artery (PA) pressure is difficult, but important, to estimate by noninvasive methods. Accordingly, numerous noninvasive methods have been used. Perhaps the most accurate noninvasive method is determination of tricuspid regurgitation velocity gradient, which estimates instantaneous difference between right atrial and ventricular systolic pressure. In the absence of pulmonary stenosis and with addition of right atrial pressure, the result can be used to approximate PA pressure.[1] Reliable recording of tricuspid regurgitation in some individuals, however, has proven difficult. Accordingly, many centers have used the inverse relations between PA pressure and PA acceleration time to predict PA pressure.[2] PA acceleration time is derived from Doppler PA velocities. Although PA acceleration time has been used to estimate PA pressure, full characterization of the measurement has yet to be determined. PA acceleration time has been reported to vary over a small range in adults (75 to 170 ms)[2] and a smaller range in children (51 to 140 ms).[3] Ranges are not truly continuous because the Doppler waveform is obtained by intermittent Fourier analysis, a method that depends on a time history of the waveform, especially for low velocities such as those inscribed at the very beginning of systole. Finally, information is unavailable to suggest whether PA acceleration time is variable for a given individual as the result of small changes in PA pressure.

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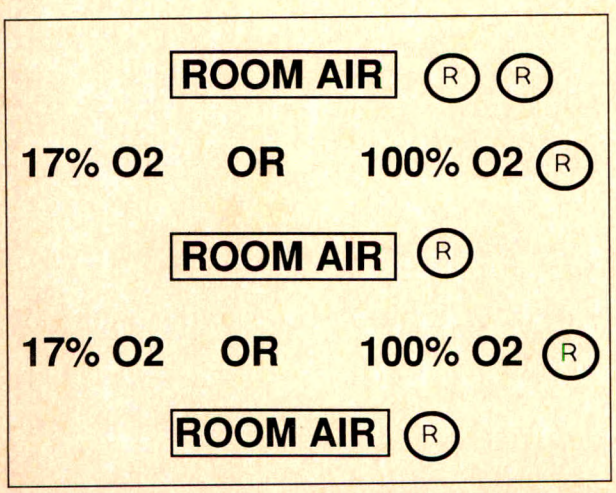


FIGURE 1. The sequence of testing is depicted. Each *circled R* represents a recording of pulmonary artery acceleration time. Sequence is from *top* to *bottom*.

Alveolar oxygen partial pressure alteration inversely affects PA pressure and vascular resistance.[4] Accordingly, increased fraction of inspired oxygen should decrease PA pressure and resistance and lengthen the PA acceleration time. Conversely, lowering inspiratory oxygen percentage below room air should increase PA pressure and resistance and shorten PA acceleration time. The hypothesis for this study is that PA acceleration time is variable for a given individual and that changes in fraction of inspired oxygen cause inverse changes in PA acceleration time.

Subjects for this study were solicited by advertisement. Eligible respondents could be men or women 20 to 35 years old who had no known cardiopulmonary disease. Informed consent was obtained from each subject for a protocol approved by the University of Arizona Human Subjects Committee. Subjects were screened by 2-dimensional echocardiography to eliminate those in whom PAs could not be imaged or interrogated. Individ-

uals with arrhythmias were also excluded. For those accepted into the study, a complete imaging echocardiogram was performed with a Biosound NDB 256 Doppler echograph operating at 2.25 or 3.5 MHz. Flow area measurements of the aortic, pulmonary and mitral valves were performed according to the methods of Loeber et al.[5] Velocities were interrogated in the central portion of the distal main PA, in the ascending aorta distal to the sinus of Valsalva and at the rings of the tricuspid and mitral valves. Velocities were recorded at a stripchart speed of 100 mm/s.

Figure 1 shows the experimental protocol. Initially, velocities distal to the 4 valves were recorded while the subject was breathing room air. Ten minutes after initial velocity recording, PA velocity interrogation was repeated. Subjects then breathed either 100% oxygen or a mixture of 17% oxygen and 83% nitrogen through a closed system for 10 minutes. Selection of initial gas was determined randomly. During the ninth of 10 minutes, while the subject was breathing the gas mixture, recordings of the 4 velocities were repeated. A 10-minute equilibration time was allowed during which subjects again breathed room air, followed by recording of the fourth PA velocity. The alternate gas was then breathed for 10 minutes; during the last minute, recordings of the 4 velocities were repeated. Following the second gas mixture, the subject was again allowed to breathe room air for 10 minutes, at which time PA velocity was recorded for the final time.

PA acceleration time was measured using an Apple Graphics system under control of the Biodata program.[5] Time resolution was 1 ms. PA acceleration time during an intervention was measured and expressed as percentage change from the preceding PA acceleration time baseline measured in room air. Two methods for heart rate correction of PA acceleration time were used: the RR interval method, whereby the PA acceleration time was divided by the square root of the RR interval, and the method of Luthy et al[6] (PA acceleration time + 0.74 [heart rate]). Mean velocity for cardiac output measurement was determined by integration of the velocity waveforms after a previously reported method.[5] Cardiac output (ml/min) was computed as the product of mean velocity (cm/s), flow area (cm^2) and time (60 s/min). Flow area, once measured, was assumed to remain constant. Cardiac output at any given time was reported as the average value of flow distal to all 4 valves.

Fourteen (5 women, 9 men) of the 23 potential subjects were entered into the study. Their ages ranged from 23 to 33 years. No adverse reactions to the protocol occurred.

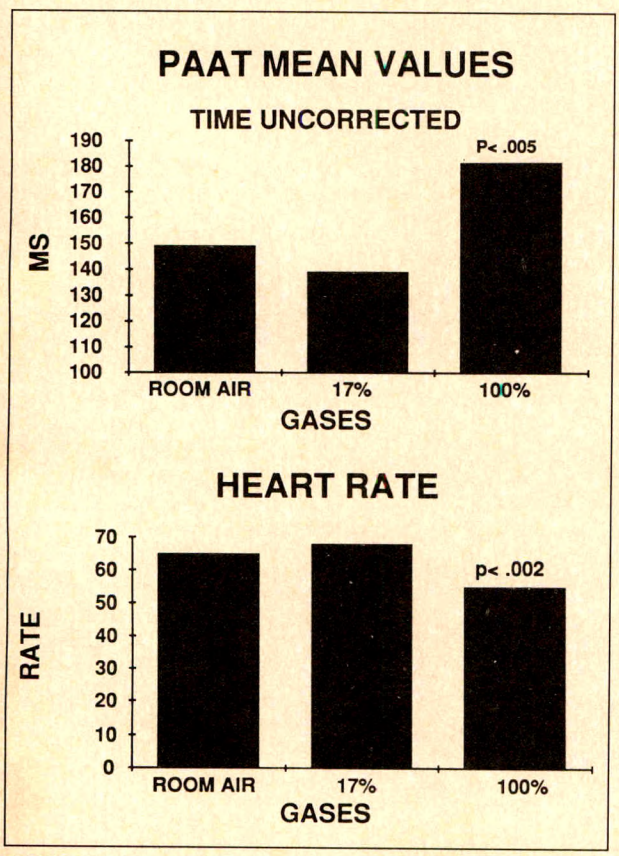


FIGURE 2. ***Top,*** **mean pulmonary artery acceleration time (PAAT) uncorrected for heart rate. Vertical axis is pulmonary artery acceleration time in ms. The oxygen concentrations of the gases are listed on the horizontal axis.** ***Bottom,*** **mean heart rate for the group is on the vertical axis and the horizontal axis depicts the oxygen percentage in the inspired air.**

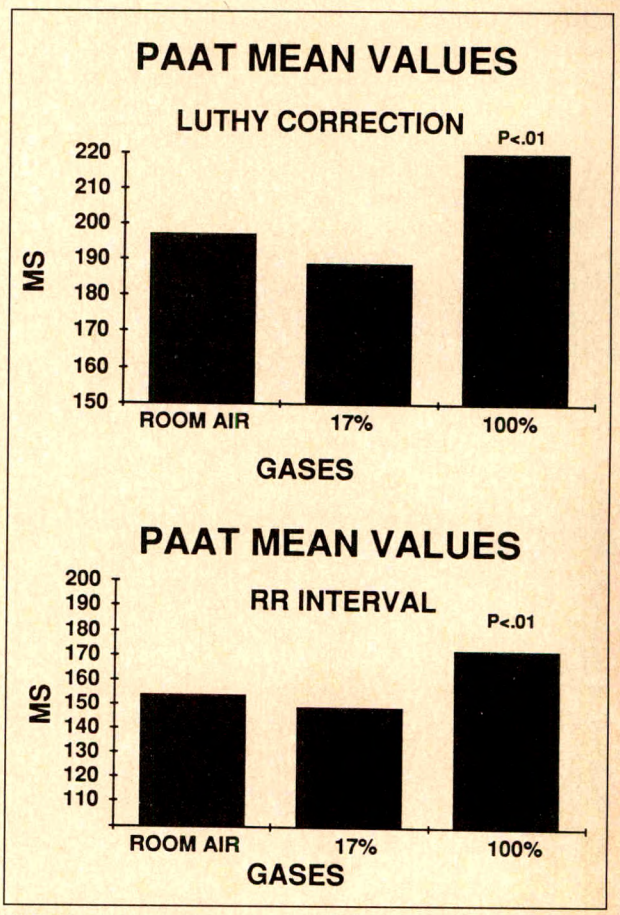


FIGURE 3. ***Top,*** **mean pulmonary artery acceleration values and the method of Luthy et al[6] to correct for adjustment of heart rate. The horizontal axis depicts the percentage of oxygen in the inspired air.** ***Bottom,*** **the RR interval technique correcting for pulmonary artery acceleration time for heart rate. The axes are the same as for the *top*.**

Analysis of variance testing showed that means of the 4 PA acceleration times recorded in each room air sequence were not significantly different ($p > 0.15$). While breathing 100% oxygen, subjects' mean PA acceleration time lengthened by 17.7%; this change was significant compared to control ($p < 0.005$) (Figure 2). However, heart rate decreased from control by a mean of 16% ($p < 0.002$) (Figure 2). Therefore, a correction for heart rate was needed. When corrected for heart rate by the Luthy method, mean PA acceleration times lengthened 12% over control ($p < 0.01$) (Figure 3). Heart rate correction by the RR interval demonstrated a mean lengthening of 11% ($p < 0.01$) (Figure 3).

Mean PA acceleration time values recorded while breathing 17% oxygen were not significantly different from the mean of control values. Correction for heart rate did not change this result.

Cardiac output, measured by Doppler, decreased a mean of 16%, from 5.7 ± 1.0 (standard deviation) liters/min while breathing room air, to 5.2 ± 0.8 liters/min while breathing 100% oxygen ($p < 0.02$). With 17% oxygen, mean cardiac output increased insignificantly to 6.0 ± 1.3 liters/min.

The 2 most important findings of this study are that: PA acceleration times for a given individual are variable, and variation in PA acceleration time can be demonstrated by comparing the value obtained during breathing of room air to that obtained during breathing of 100% oxygen. Observed changes in PA acceleration time were not due to changes in heart rate because the variation remained after heart rate correction. Further, the variation in PA acceleration time was not due to change in cardiac output.

Although our data showed significant PA acceleration time lengthening when breathing 100% oxygen, PA acceleration time shortening did not occur when breathing 17% oxygen. We speculate that a possible reason for lack of change when breathing 17% oxygen is that subjects were acclimated to the relatively high altitude of Tucson, Arizona (2,500 to 3,000 feet with an average atmospheric pressure of 702 mm Hg). Merely simulating an altitude of 5,000 feet may have been inadequate to evoke a response in this group.

Although PA acceleration time lengthened significantly with 100% oxygen, the absolute mean change of 32 ms for subjects evaluated at our altitude was small. This confinement of the PA acceleration time range of values is consonant with findings of a small range of values in prior reports that evaluated differences in PA acceleration time for normal subjects and patients with PA hypertension.[2,3] Prior investigators also found a relatively small PA acceleration time difference in these 2 groups.

We conclude that PA acceleration time lengthens significantly from baseline during administration of 100% oxygen. However, we were unable to confirm a significant decrease in PA acceleration time for our population during simulation of a change in altitude from approximately 3,000 to approximately 5,000 feet.

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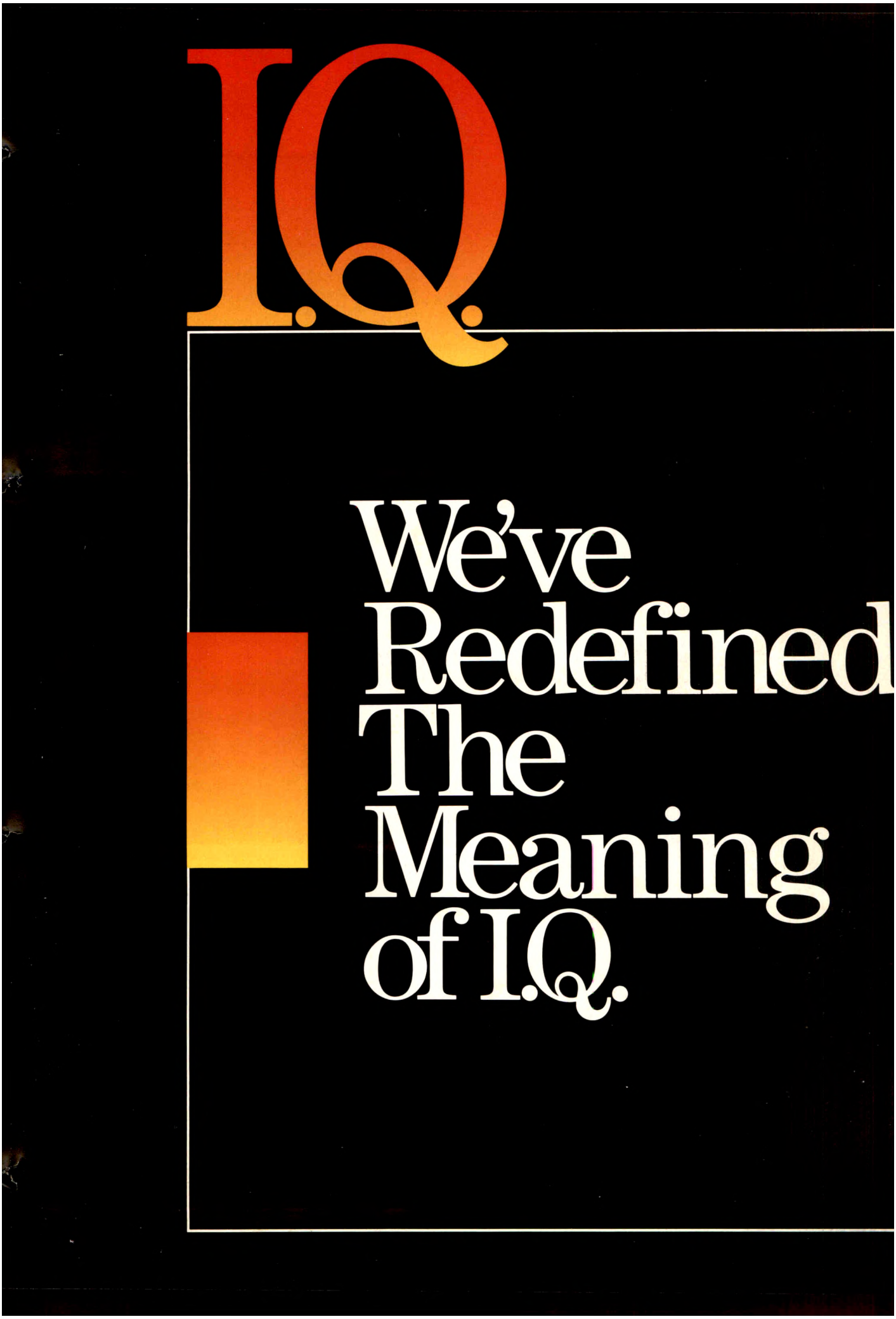
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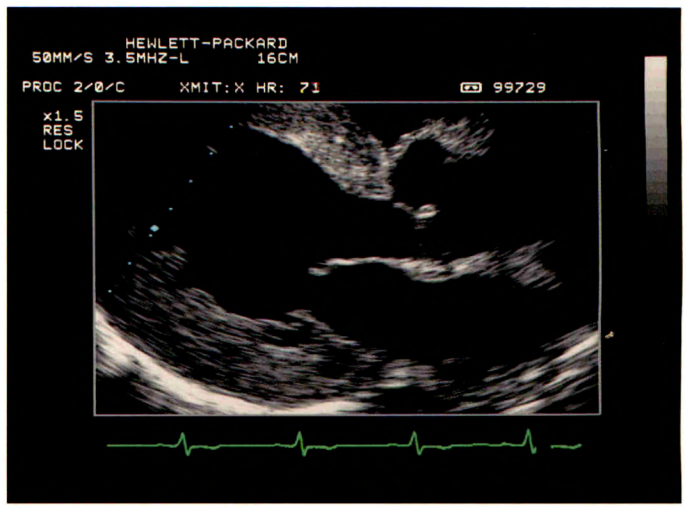
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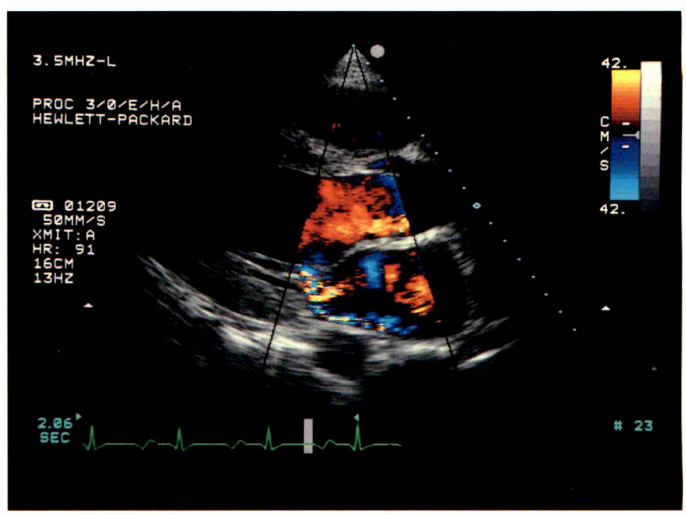
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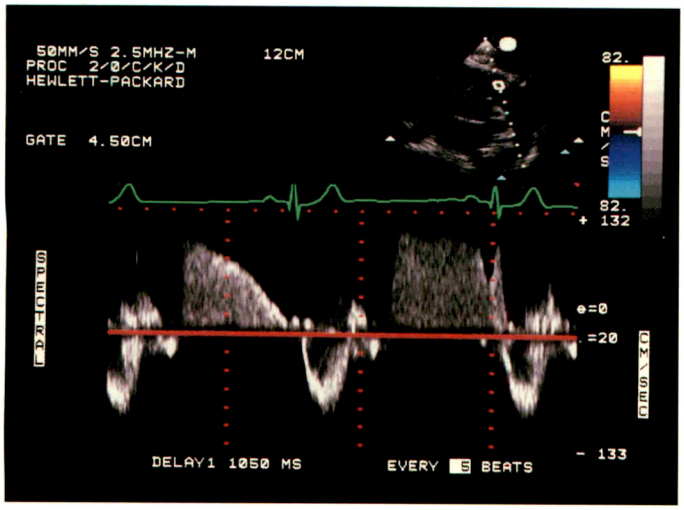


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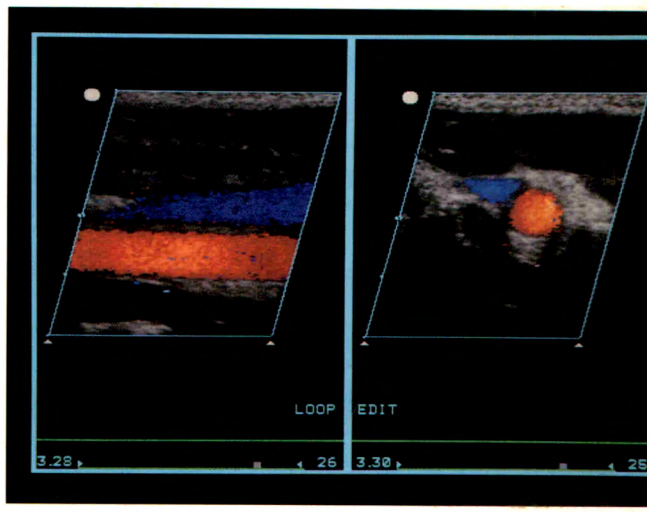


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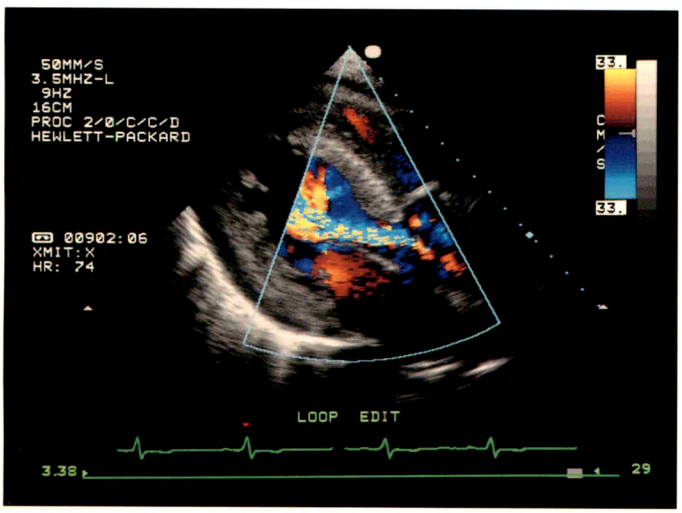
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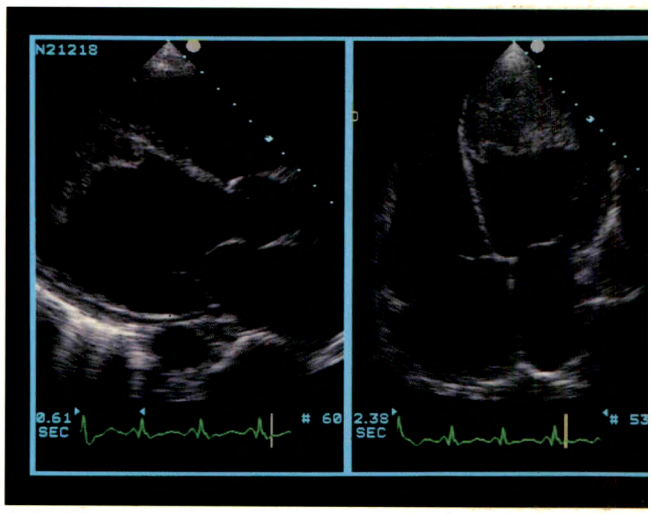
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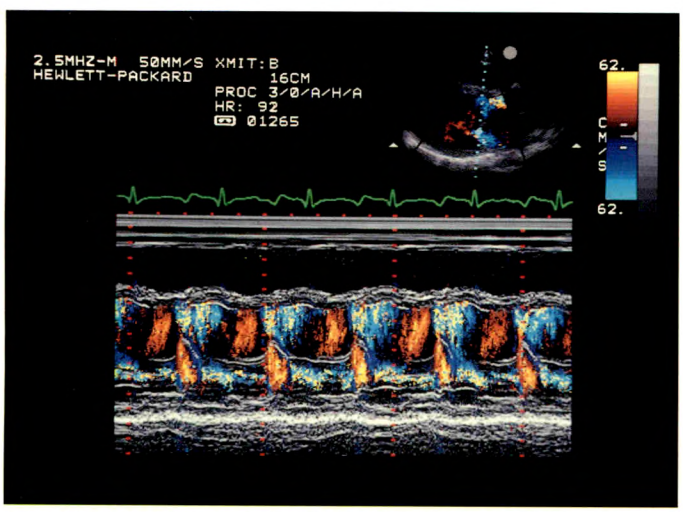
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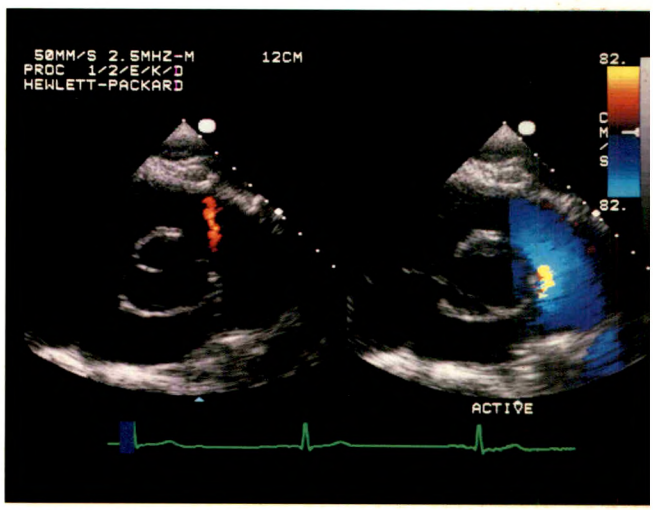
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Acute Myocardial Infarction with Normal Coronary Arteries Associated with Acetylcholine-Induced Vasoconstriction in the Absence of a Positive Ergonovine Test

Charles B. Treasure, MD, Joseph A. Vita, MD, David A. Cox, MD, R. David Fish, MD, Andrew P. Selwyn, MD, R. Wayne Alexander, MD, PhD, and Peter Ganz, MD

A small but important percentage of patients presenting with acute myocardial infarction are found to have angiographically normal epicardial coronary arteries.[1] Coronary embolism has long been thought to cause infarction in these circumstances. Thrombosis or coronary spasm at sites of angiographically inapparent atherosclerotic plaques has also been observed.[2,3] Recent studies suggest that coronary endothelial dysfunction in atherosclerosis may contribute to the predisposition both for coronary vasospasm as well as for coronary thrombus formation.[4,5] The integrity of at least 1 aspect of endothelial function, that mediating vasodilation, can now be assessed in vivo by the intracoronary administration of acetylcholine, an agent that dilates arteries indirectly by releasing endothelium-derived relaxing factor and directly constricts arterial smooth muscle when endothelium is denuded or dysfunctional. We present the history of a young man with 2 myocardial infarctions in whom diagnostic coronary arteriography and ergonovine testing failed to reveal abnormalities but acetylcholine testing provided evidence of coronary endothelial dysfunction that may have contributed to the infarctions.

A 20-year-old man was admitted for angina after a myocardial infarction. At age 17, he was hospitalized for prolonged chest pain and an anterior wall myocardial infarction evolved (peak creatinine kinase 268 mU [normal <80 mU]; 12% MB) (Figure 1). Catheterization revealed angiographically normal coronary arteries and mild anteroapical hypokinesis. At age 20, he was again hospitalized with prolonged chest pain and a lateral wall myocardial infarction evolved (creatinine kinase 744 mU; 7% MB) (Figure 2). A test for cocaine metabolites was negative. He was discharged receiving verapamil. Three weeks later, angina recurred and he was admitted for evaluation. He had no coronary risk factors or history of illicit drug use. Physical examination was normal. Total cholesterol was 118 mg/dl; high density lipoprotein was 42 mg/dl. Sedimentation rate, antithrombin III, protein C, protein S, endogenous tissue plasminogen activator and plasminogen activator inhibitor were normal. The electrocardiogram showed nonspecific ST-T wave changes. Routine arteriography revealed normal coronary arteries without any luminal narrowing (Figure 3A).

After informed consent was obtained (and vasoactive medications were withheld), the functional behavior of his epicardial coronary arteries and his vasodilator reserve was evaluated. In the left anterior descending coronary artery, serial 2-minute infusions of agents were administered via a Doppler catheter as follows: control, acetylcholine 10^{-8}, 10^{-7} and 10^{-6} M, recontrol, adenosine 10^{-6}, 10^{-5} and 10^{-4} M and recontrol. Lastly, the patient received ergonovine in graded doses of 0.05, 0.10 and 0.20 mg intravenously. Results of the coronary arteriograms were analyzed quantitatively to assess changes in the left anterior descending coronary artery diameter in response to drug infusions and to ob-

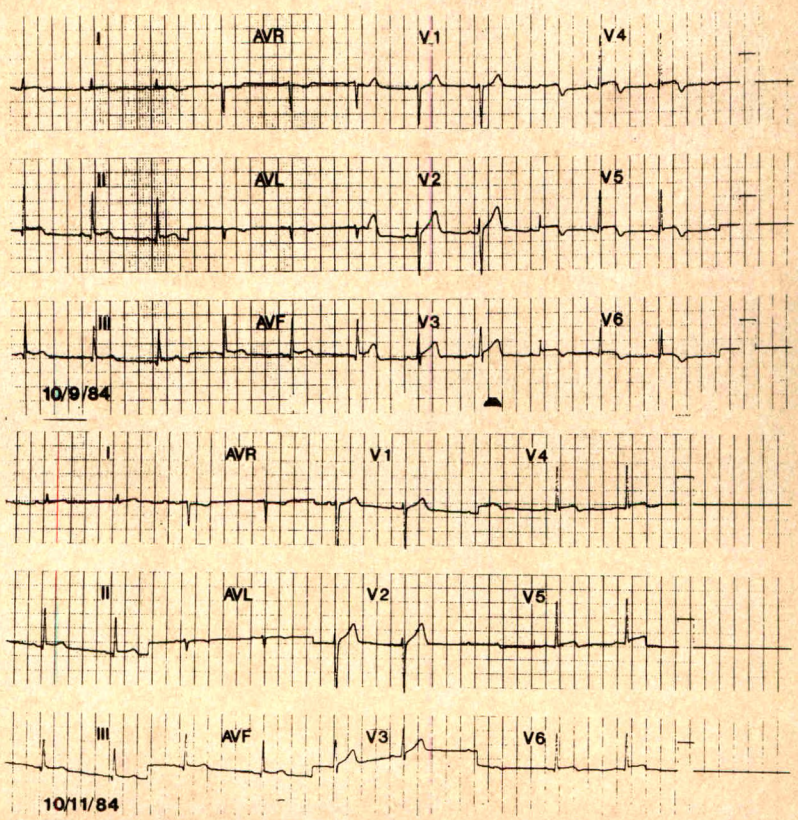


FIGURE 1. Initial and subsequent electrocardiograms showing evolution of first infarction (age 17).

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tain a cross-sectional area at the Doppler tip to convert flow velocity to blood flow.

Ergonovine resulted in no pathologic focal constriction (3% left anterior descending coronary artery maximal diameter constriction) (Figure 3B). Adenosine resulted in a 54% increase in left anterior descending coronary artery diameter, consistent with intact epicardial smooth muscle dilation and a 5.6-fold increase in blood flow, demonstrating normal dilator reserve. Acetylcholine produced dramatic coronary constriction (45% left anterior descending coronary artery maximal diameter constriction) (Figure 3C).

Commonly, patients who present with a suspicion of myocardial ischemia and angiographically normal coronary arteries undergo ergonovine testing in an effort to provoke coronary spasm. Ergonovine testing may not address other potential vascular mechanisms of myocardial ischemia such as endothelial dysfunction. Recently, the importance of endothelium in the control of vascular tone has been appreciated. Many agents, including acetylcholine, have been shown to relax blood vessels indirectly by stimulating release from the endothelium of endothelium-derived relaxing factor. Endothelial damage could result in diminished endothelium-derived relaxing factor production leading to vasospasm.

Although coronary vasospasm may be playing an etiologic role in this patient, the results of acetylcholine testing should not be construed to signify that vasospasm is the only explanation for his myocardial ischemia. The endothelium has other important roles. Its property as a nonthrombogenic surface is partially mediated by production of tissue plasminogen activator, endothelium-derived relaxing factor and prostacyclin. Under pathologic conditions, the endothelium can become procoagulant,[5] which could predispose the patient to intracoronary thrombosis.

Although young age coupled with the absence of coronary risk factors place this patient at low risk for atherosclerotic coronary artery disease, his history of recurrent myocardial ischemia and his marked coronary constrictor response to acetylcholine could be consistent with premature, angiographically inapparent atherosclerosis. Early evidence of athero-

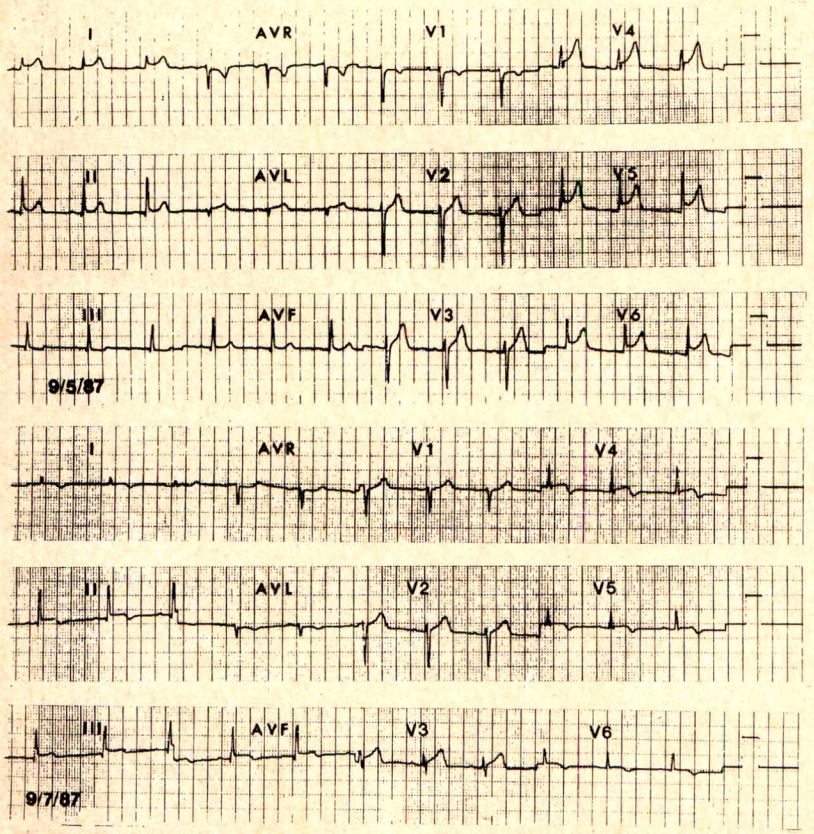


FIGURE 2. Initial and subsequent electrocardiograms showing evolution of second infarction (age 20).

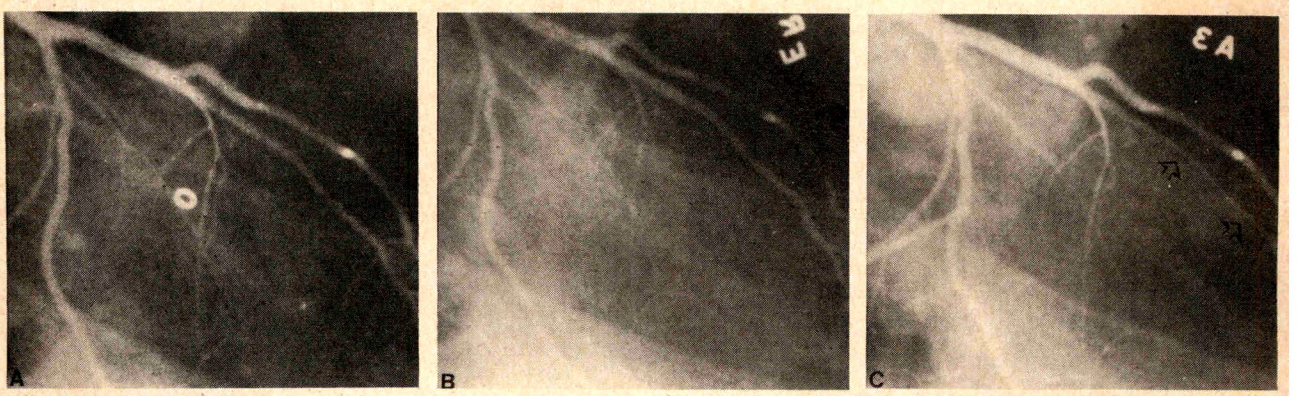


FIGURE 3. *A*, initial left coronary arteriogram demonstrating normal coronary arteries without any luminal irregularities. *B*, left coronary arteriography after serial intravenous administration of 0.05, 0.10 and 0.20 mg of ergonovine demonstrating diffuse, mild constriction but no pathologic focal constriction (3% decrease in left anterior descending coronary artery diameter in the most constricting segment). *C*, left coronary arteriography after serial intracoronary administration of 10^{-8}, 10^{-7} and 10^{-6} M acetylcholine demonstrating severe and paradoxical constriction of the left anterior descending coronary artery (*arrows*).

sclerosis among young men was noted in 6% of Korean War casualties.[6]

Frequently, in patients with myocardial infarction and normal coronary arteries, provocative testing is inconclusive and therapy is empiric. In a young man with no angiographic evidence of coronary narrowings, a negative ergonovine test but an unquestionable history of recurrent myocardial ischemia, we have observed evidence of deranged endothelial function. This endothelial abnormality may be related to occult coronary atherosclerosis. It may also predispose to vasospasm or thrombosis. Further characterization of this endothelial abnormality may lead to a better understanding of mechanisms of myocardial ischemia in the setting of normal coronary arteries.

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Balloon Occlusion of an Internal Mammary Artery to Anterior Interventricular Vein Fistula

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An infrequent complication of coronary artery bypass grafting (CABG) is inadvertent grafting to a coronary vein resulting in an arteriovenous fistula. We describe a case in which the left internal mammary artery (IMA) was anastomosed to the anterior interventricular vein. To our knowledge, this is the first report involving such a fistula managed with balloon occlusion.

The patient was a 66-year-old man who had had 4-vessel CABG in 1972. Because of recurrent angina he underwent coronary angiography and was found to have severe coronary artery disease and occlusion of all his grafts. The following month he underwent repeat 4-vessel CABG, with the left IMA used to bypass the left anterior descending coronary artery. Two weeks after discharge he noted recurrence and progression of angina, which prompted readmission. Repeat coronary angiography showed the native coronary circulation to be unchanged. The saphenous vein bypass grafts to the obtuse marginal and right coronary artery were patent. The diagonal graft had a 90% obstruction at its distal anastomosis. With dye injection into the left IMA, there was no filling of the left anterior descending coronary artery but direct filling of the anterior interventricular vein with rapid

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Manuscript received August 17, 1989; revised manuscript received and accepted August 28, 1989.

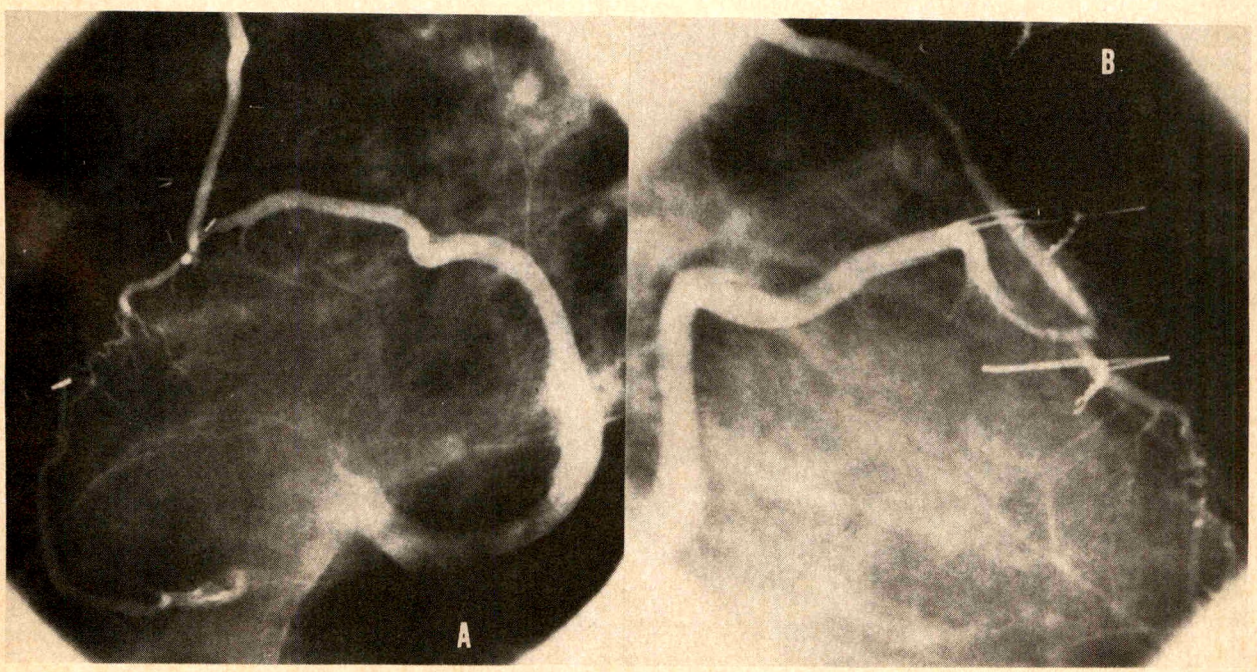


FIGURE 1. Left lateral (*A*) and right anterior oblique (*B*) views showing anastomosis of the left internal mammary artery to the midportion of the anterior interventricular vein with opacification of the coronary sinus.

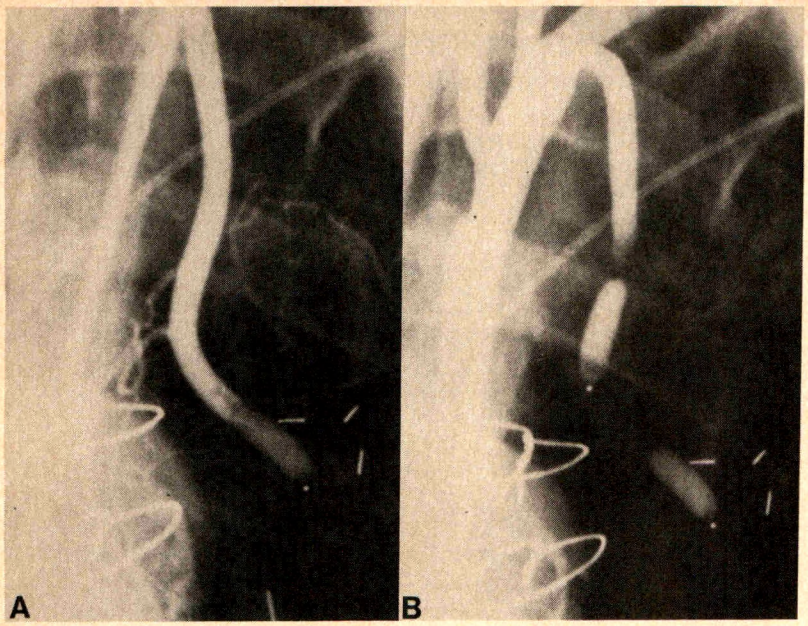


FIGURE 2. Anteroposterior angiographic view showing complete occlusion of the fistula after release of the first (*A*) and second (*B*) balloons in the left internal mammary artery.

washout into the coronary sinus (Figure 1). The pulmonary artery oxygen saturation was 66% and the shunt was judged to be small.

After surgical consultation it was felt that the patient was at high risk for another CABG. The next week the patient underwent successful percutaneous transluminal coronary angioplasty of the diagonal graft lesion. Immediately after angioplasty, an 8Fr IMA bypass guide (Shiley) was positioned in the left IMA. A no. 16 (0.6 cc) Debrun latex balloon (Ingenor), tied to the distal end of a 2Fr polyethylene catheter with elastic ligatures, was introduced through the guide. The flow-directed balloon was positioned at the middle third of the left IMA, inflated with iopamidol diluted 1:1 with saline, and then released. Coronary sinus oxygen saturation decreased from 74 to 38% and angiography showed complete occlusion of the fistula (Figure 2A). A second balloon was placed proximal to the first balloon (Figure 2B). At discharge the patient's symptoms were improved and this benefit persisted at 1-month follow-up.

The few reported cases of iatrogenic coronary arteriovenous fistulas have all involved saphenous vein bypass grafts. We and others have shown that it is possible to manage this subset of patients without surgery. After successful angioplasty, Goldbaum et al[1] used Gianturco coils to occlude a vein graft anastomosed to the anterior interventicular vein. Grollman et al[2] applied selective coil embolization as the sole treatment in a patient whose presentation was congestive heart failure. Recently, Jost et al[3] were the first to describe the use of a silastic balloon to occlude a vein graft to the anterior interventricular vein after performing staged angioplasty.

Various devices and materials have been used to occlude vessels. Liquid and particulate matter, however, are unsuitable for coronary arteriovenous fistulas because of the risk of materials migrating into the venous system producing pulmonary embolization or thrombosis. Coil embolization in such situations has been successfully applied.[1,2] Balloon embolization, such as that used in this case, offers a unique advantage over the coil because it can be precisely positioned before detachment and occlusion is immediate (not dependent on clotting). However, instances of balloon migration have resulted from premature detachment[4] or partial deflation soon after release.[5] This problem can be reduced with the double balloon technique. A proximal balloon can be inflated temporarily[4] or permanently[5] to protect the distal balloon from the pressure and turbulent flow, which tends to promote premature detachment. With time, the balloon deflates as contrast media leak out. However, the fistula almost always remains closed secondary to thrombosis and fibrosis.[6] In summary, in selected cases an iatrogenic coronary arteriovenous fistula can be managed successfully with selective balloon occlusion when technical difficulties and high risk preclude repeat CABG.

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Saphenous Vein Graft Angioplasty in a Teenager

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Percutaneous transluminal coronary angioplasty (PTCA) is a widely used technique for the elective and emergent revascularization of obstructive coronary artery disease. Due to the increasing frequency of atherosclerosis with age, PTCA has been practiced exclusively in an adult population.[1] Although the field of interventional pediatric cardiology has grown tremendously in recent years,[2] PTCA has not been reported in this age group. We recently performed PTCA in a teenager; to our knowledge this is the youngest patient reported to benefit from this evolving technique.

A 15-year-old girl was diagnosed in infancy with anomalous origin of the left main coronary artery from the pulmonary trunk. At age 9 months she underwent surgical ligation of the left coronary artery origin. She did well until age 10, when she developed exertional anginal symptoms. Coronary artery bypass surgery using a reverse saphenous vein graft to the left main stump was performed. The patient subsequently did well until age 15 when she again began to experience anginal symptoms with exertion. The patient underwent a maximal exercise stress test with thallium-201 tomography. Tomographic images revealed reversible perfusion defects anteriorly at the apex and laterally in the apical and midventricular sections, consistent with ischemia of both the left anterior descending and left circumflex arteries. Angiography demonstrated a 70% anastomotic stenosis with a lucent appearance (Figure 1). A 4.0 mm Simpson Ultra Low Profile II balloon catheter (Advanced Cardiovascular Systems) and a 0.014 inch hi torque floppy guidewire (Advanced Cardiovascular Systems) were steered into the vein graft and through the stenosis into the left circumflex artery. The balloon was positioned in the anastomosis and several inflations were performed for up to 60 seconds and 6 atmospheres of pressure (Figure 2).

From Cardiovascular Consultants, Inc., 4320 Wornall Road, Medical Plaza II-20, Kansas City, Missouri 64111. Manuscript received September 18, 1989, and accepted September 24.

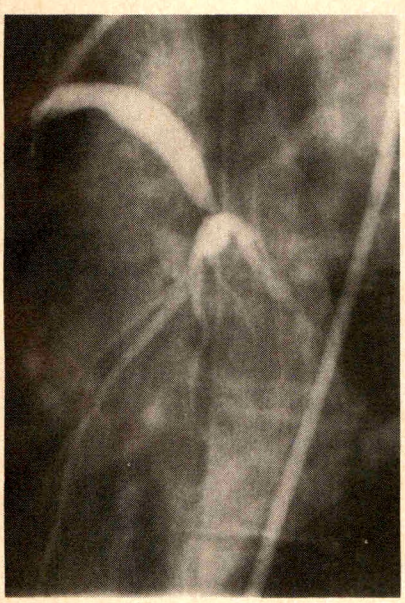


FIGURE 1. Selective injection of the saphenous vein graft to the left main stump in the 15-year-old female patient. In this left anterior oblique projection, a lucent zone at the graft anastomosis is apparent, and the anastomosis is 70% narrowed in a band-like manner.

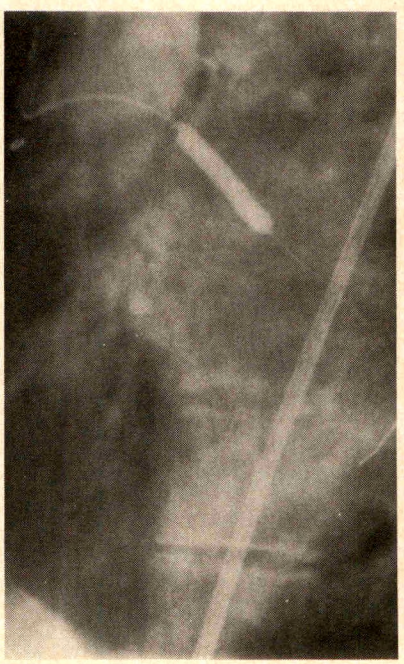


FIGURE 2. Placement of the balloon catheter across the stenotic region with full balloon expansion is demonstrated. The guidewire is in the left circumflex artery.

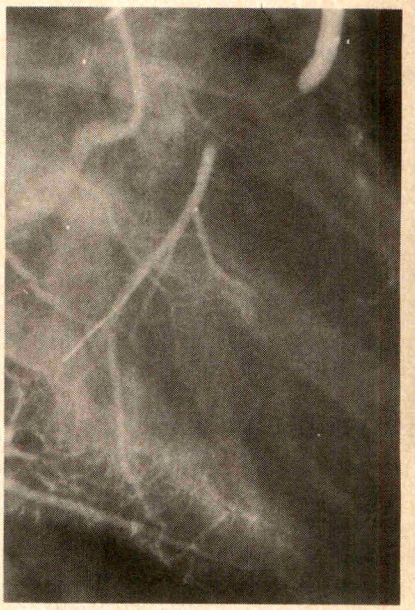


FIGURE 3. Selective injection of the right coronary artery using a separate coronary catheter during balloon inflation in the vein graft anastomosis. In this right anterior oblique projection, persistent collateral flow from the right system to the left circumflex artery is apparent.

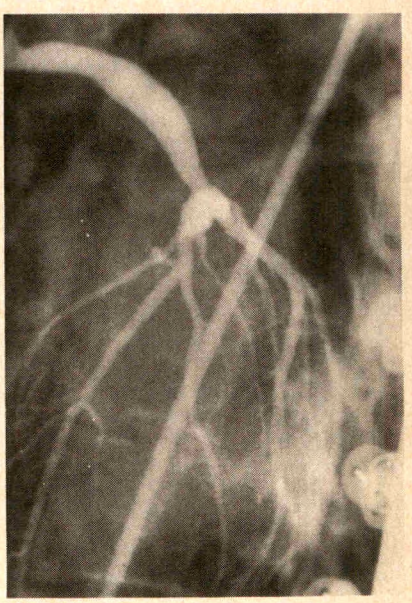


FIGURE 4. Final selective injections after balloon angioplasty demonstrated wide patency of the anastomosis with good distal run-off.

During balloon inflation, the right coronary artery was selected with a diagnostic catheter and was injected (Figure 3). Persistent collateral flow from the right coronary artery to the left circumflex artery was observed (Figure 3). With the balloon catheter and guidewire withdrawn, final angiograms revealed markedly improved patency and good flow through the area (Figure 4). The distal anastomosis appeared to be at least as large as the left main artery. The next day the patient underwent repeat exercise thallium-201 tomography. Tomographic images after stress and 4-hour redistribution were normal by visual and quantitative analysis. At 8-month follow-up, she continues to do well, is free of chest pain and has no limitations of her activities.

The patient described had anomalous origin of the left main coronary artery from the pulmonary artery, referred to as the Bland-Garland-White syndrome.[3] Survival into adulthood is dependent on the development of collaterals between the right coronary artery and the left arterial system (Figure 3), and flow through the anomalous left main artery is retrograde. The anomalous left main artery produces a steal phenomenom from the right coronary artery and produces a large mass of ischemic myocardium. Although a number of surgical approaches to correct this condition have been described, ligation of the left main artery and construction of a bypass graft from the aorta to the left main artery or to the left anterior descending artery have been performed most frequently[4] with good relief of symptoms. In our patient this approach led to initial relief of symptoms followed by recurrent angina after an interval of 5 years. Angiography revealed a constriction at the anastomosis of the vein graft with the left main coronary artery, presumably due to surgical technique or intimal thickening. PTCA appeared to be an attractive alternative to repeat cardiac surgery in this young patient. A large balloon catheter (4.0 mm) was used to accommodate the dimensions of the vein graft and the left main stump. We have previously described simultaneous inflation of 2 balloon catheters in oversized vein grafts, known as hugging balloons[5]; however, we believe that the result following single balloon inflations had restored the diameter of the anastomosis to that of the left main stump.

We expect that the problems experienced by this young patient will be seen more often in the future as patients with congenital heart disease survive for longer periods because of more aggressive therapies. Young patients with anomalous origin of the left coronary arterial system from the right sinus of Valsalva[6] provide another population that during follow-up may require PTCA.

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Surgical Correction of Pulmonary Atresia with Ventricular Septal Defect and No Central Pulmonary Arteries

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As recently as 1988 patients with pulmonary atresia with ventricular septal defect and no central pulmonary arteries were dismissed as having "no prospect of complete repair."[1] We report our experience in the management and successful staged repair of this anomaly in a 4½-year-old child.

PS was cyanotic at birth and diagnosed as having pulmonary atresia with ventricular septal defect and no central pulmonary arteries. All 19 bronchopulmonary segments were perfused by collateral arteries and a patent ductus arteriosus (Figures 1A, B, and 2A). A 5-mm Gortex graft was placed from the left innominate artery to the confluence of the left lobar pulmonary arteries (Figures 1D and 2B). At 3 years of age, angiography showed a functioning shunt and 2 stenotic aortopulmonary collateral arteries, which provided the major blood supply to the right lung. Pressure distal to the stenosis was 28/18 mm Hg, and aortic oxygen saturation was 73%. A 6-mm Gortex graft was placed from the right subclavian artery to right lower and upper lobe collateral arteries as they entered the lung parenchyma (Figures 1C and 2B). At 4 years of age, an angiogram showed that both shunts were functioning. The aortic oxygen saturation was 82%, and the ratio of pulmonary to systemic blood flow (QP/QS) was 1.4/1. Fourteen bronchopulmonary segments were perfused via the shunts. An additional large pulmonary artery supplied a portion of the right upper lobe. At surgery, this artery was identified in the fissure between the upper and middle lobes. A 10-mm Gortex graft was attached to it and to the previous 6-mm graft (Figure 2C). A 20-mm aortic homograft was used to connect the right ventricle to the lobar pulmonary arteries on the left. A side arm of 12-mm Gortex graft connected the homograft to the 10-mm graft on the right (Figures 2D and 3). The ventricular septal defect was closed and the systemic-pulmonary shunts were ligated. Postoperatively, right/left ventricular systolic pressure ratio was 0.45. There was a small residual ventricular septal defect. The patient is doing well 19 months postoperatively.

This report adds another patient to 2 previously reported[2] who have undergone successful repair of pulmonary atresia with ventricular septal defect and no central pulmonary arteries. All 3 had the majority of bronchopulmonary segments perfused by systemic arteries and large

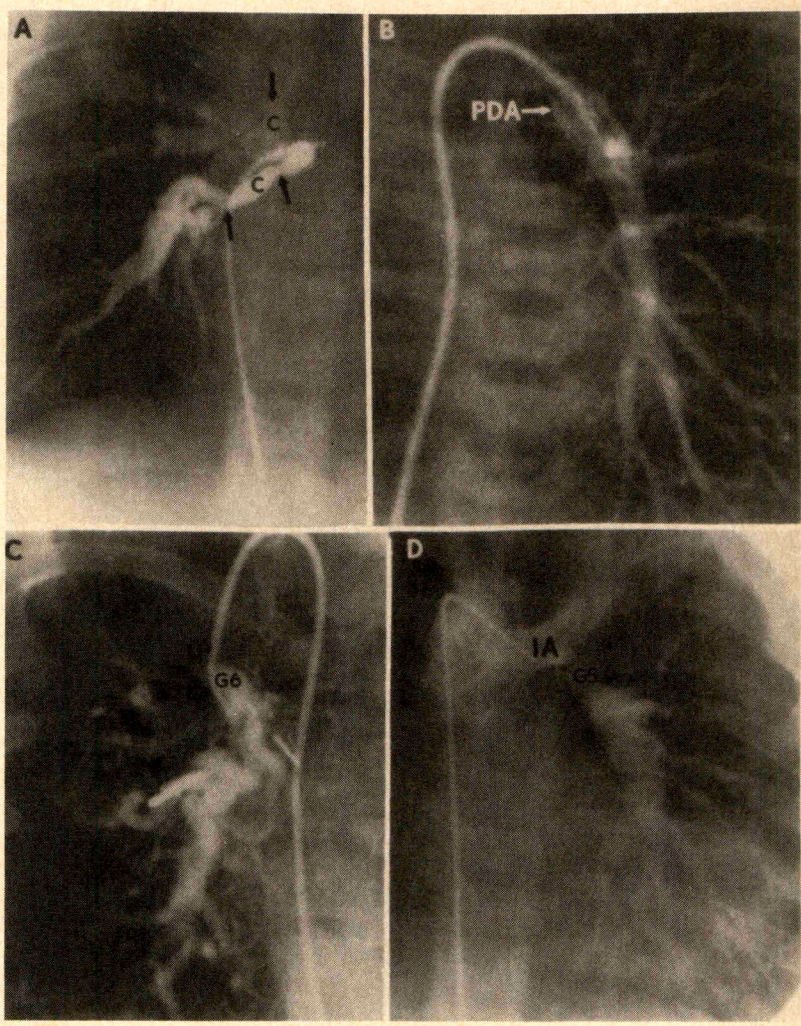


FIGURE 1. Selective contrast angiography, frontal views. *A*, preoperative right-sided aortopulmonary collateral (c) injection. Several areas of stenosis are indicated (*arrows*). In this projection and the corresponding lateral, 10 bronchopulmonary segments were identified. *B*, preoperative left pulmonary artery injection via the patent ductus arteriosus (PDA). Nine bronchopulmonary segments were identified. *C*, right Gortex graft injection after unifocalization. Six bronchopulmonary segments were seen. *D*, left Gortex graft injection. Eight bronchopulmonary segments were seen. G5 = 5 mm Gortex graft; G6 = 6 mm Gortex graft; 1A = innominate artery.

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lobar pulmonary arteries accessible for unifocalization. In our patient, 14 of 19 bronchopulmonary segments could be identified before repair. The first patient of Barbero-Marcial et al[2] had 4 aortopulmonary collateral arteries and at least 16 of 19 bronchopulmonary segments were perfused. Their second patient had 3 aortopulmonary collateral arteries perfusing all 19 bronchopulmonary segments. Our patient had high aortic oxygen saturation and QP/QS, evidence that the lobar pulmonary arteries were of adequate size for repair.[3] The normal pressure in the right lower lobe pulmonary artery was evidence against pulmonary vascular disease. The first patient reported by Barbero-Marcial et al[2] presented at 18 months of age with

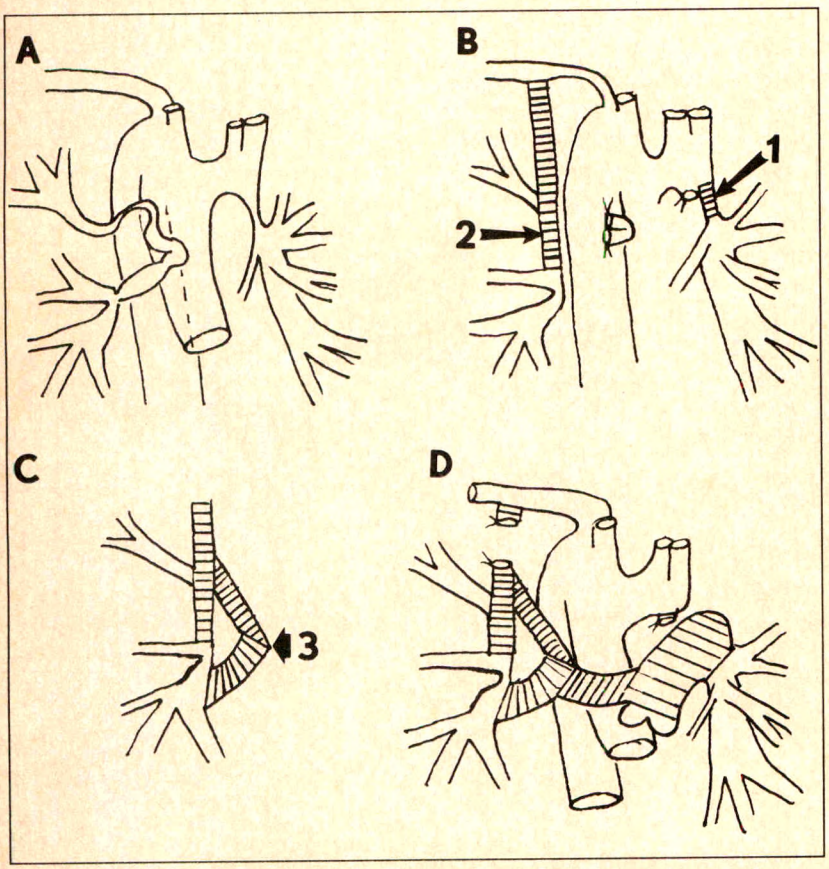


FIGURE 2. Artist's drawings illustrating preoperative and postoperative pulmonary blood supply. *A*, preoperative. See Figure 1A and B. *B*, postoperative left (1) and right (2) Gortex shunts. See Figure 1C and D. *C*, postoperative insertion of second Gortex graft (3) on right. *D*, postoperative repair with right ventricular outflow tract reconstruction by aortic homograft. See Figure 3.

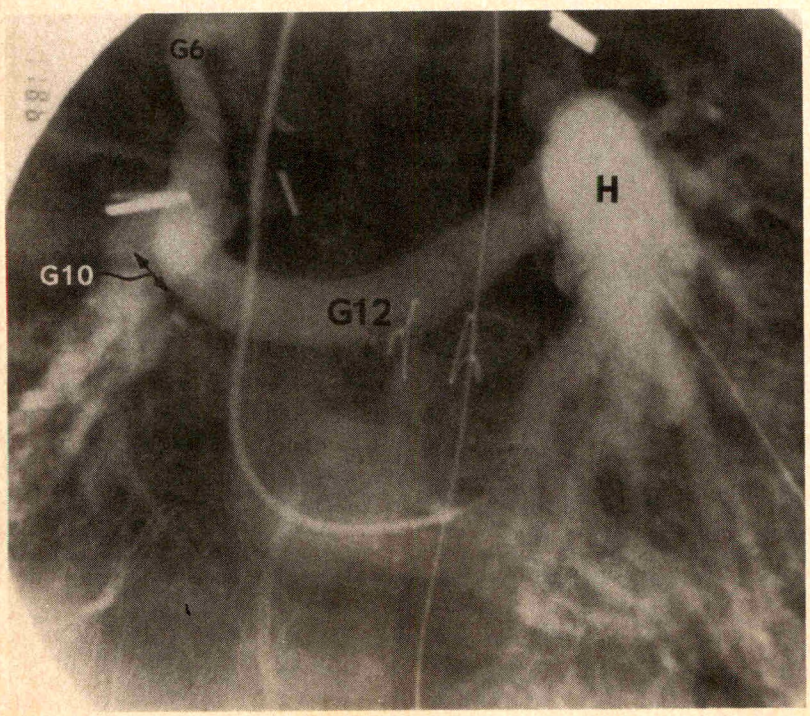


FIGURE 3. Selective contrast injection, right ventricle, frontal view, postoperative repair. A 20 mm aortic homograft (H) was anastamosed directly to the confluence of lobar pulmonary arteries on the left. A side arm of 12-mm Gortex graft (G12) was used to connect the homograft to the 10-mm Gortex graft (G10) on the right. G6 = 6-mm Gortex graft.

congestive heart failure, evidence for increased pulmonary blood flow and large pulmonary arteries. In all 3 patients a staged surgical approach replaced systemic collateral arteries with grafts to supply adequate but controlled perfusion, promote growth of the pulmonary arteries and protect against pulmonary vascular disease. Unifocalization simplified establishing perfusion from the newly constructed right ventricular outflow tract at repair. Angiography between procedures helped refine the surgical approach. By utilizing the newly created aortopulmonary connections, it was possible to define the sources of pulmonary perfusion better than at the initial study. Postoperative evaluation showed perfusion of the majority of bronchopulmonary segments and acceptable right/left ventricular systolic pressure ratios. The clinical results were good in all 3 patients.

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A Transmural Approach for Endocardial Ventricular Pacing

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The 2 standard approaches to placement of cardiac pacemaker leads are epicardial leads applied at thoracotomy and endocardial leads placed transvenously. At times, the usual transvenous approaches are not feasible, such as in superior vena cava obstruction or impaired access to the right ventricle because of tricuspid stenosis or a mechanical prosthetic valve. Usually, such situations necessitate epicardial pacing, which sometimes is unsatisfactory because of poor thresholds or inadequate sensing with epicardial leads. We present a case in which a new method for endocardial ventricular lead placement was used when both standard endocardial pacing and epicardial pacing were unsatisfactory.

A 63-year-old woman had Starr-Edwards prosthetic valves in aortic, mitral and tricuspid positions. At age 59 she had developed complete heart block with a ventricular escape rate of 30 beats/min that required epicardial lead placement because of the prosthetic tricuspid valve. Positioning of the lead was difficult because of high thresholds. During follow-up, the patient developed failure to capture, but her intrinsic heart rate had increased to 50 beats/min. The patient was asymptomatic over the following 4 years. In 1988, the patient presented with progressive dyspnea and fatigue. Electrocardiographic and pacemaker analysis revealed complete heart block with a ventricular rate of 30 beats/min and failure to capture despite maximal energy settings (8.1 V at 0.92-ms pulse width).

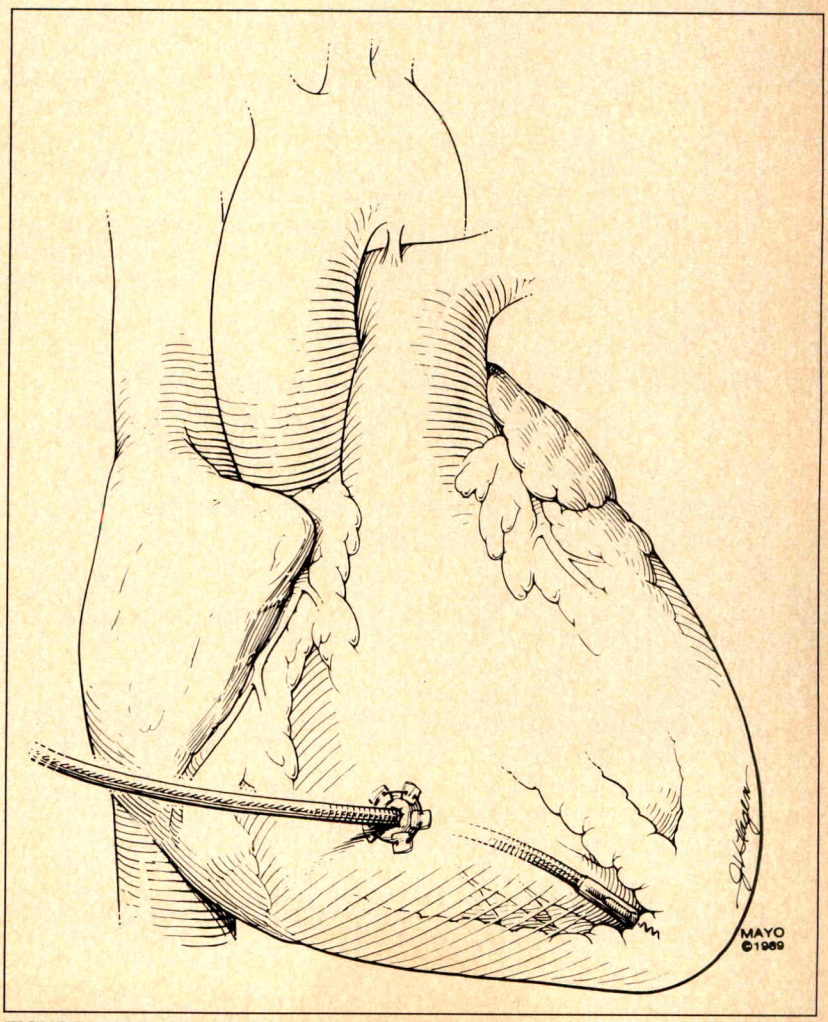


FIGURE 1. Transmural ventricular lead placement. Ventricular endocardial lead is passed through right ventricular wall and actively fixated to right ventricular endocardium. A purse string suture secures lead in right ventricular free wall. (By permission of Mayo Foundation.)

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Manuscript received April 24, 1989; revised manuscript received and accepted September 1, 1989.

Lead impedance measured >2,500 ohms.

At operation to investigate the pacemaker system, the generator functioned normally. The electrode-myocardial interface sites were markedly fibrotic. The ventricle was covered with a thick layer of epicardial fat, and multiple attempts to find adequate thresholds with 3-turn screw-in epicardial leads failed. A platinized "fishhook" epicardial lead (Medtronic 4951-P) was placed with a threshold of 2 V, but adequate thresholds for a second 4951-P lead could not be achieved. An active-fixation endocardial lead (Medtronic 6957) was then placed through the anterior wall of the right ventricle with the Seldinger technique and a 10Fr peel-away introducer sheath. The screw-in unipolar endocardial lead tip was directed toward the apex of the right ventricle and fixated (Figure 1). Good thresholds were obtained (0.8 V at 0.6-ms pulse width). The insertion site through the right ventricular wall was secured with a pledgeted purse string suture of 3-0 Prolene.

The threshold in a bipolar configuration (endocardial lead negative, epicardial lead positive) was 1.2 V at 0.6-ms pulse width. The 2 leads were brought out through the subcostal area and connected to an activity-sensing, rate-modulating pulse generator (Medtronics 8402).

The postoperative course was uncomplicated. At follow-up 3 months later, she had a pulse-width threshold of 0.25 ms at a 5-V setting. One year after operation, she was active and asymptomatic.

Endocardial lead placement tends to offer easier placement, lower morbidity and more reliable thresholds than epicardial lead systems.[1,2] Yet, situations arise in which the usual transvenous approach is inconvenient or not possible and epicardial pacing is inadequate. In the case presented, a prosthetic tricuspid valve was in place and attempts at epicardial pacing failed because of a fibrotic, fatty epicardium. A ventricular endocardial lead was placed through the wall of the right ventricle without complication and with good sensing and pacing thresholds. This is the first documented case of transmural ventricular pacing. The precedent for transmural endocardial pacing comes from atrial lead systems placed transmurally that demonstrated good function and stability.[3,4]

The theoretical problems of using the transmural approach might include: the infeasibility of removing the lead percutaneously (e.g., if the lead were infected or had perforated the ventricular wall); the possibility of mural scarring and increased arrhythmias; lead dislodgment, lead fracture or lead perforation, which could result because the lead is tethered in the right ventricular free wall; and the risk of transmural hemorrhage, especially if the patient has received anticoagulants.

In view of these possible disadvantages and the lack of long-term follow-up in our patient, the transmural approach to endocardial pacing should be considered only after standard approaches fail. In the case presented, transmural endocardial pacing, at least in the short term, offered good lead stability and excellent thresholds and sensing.

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Severe Stenosis Involving a Congenitally Bicuspid Aortic Valve in the Tenth Decade of Life

Dean G. Karalis, MD, Jeffrey M. Wahl, MD, Gary S. Mintz, MD, and Krishnaswamy Chandrasekaran, MD

A congenitally bicuspid aortic valve (BAV) is present in at least 1% of persons.[1] The most common complication of a BAV is stenosis, and this congenital malformation represents the most common cause of isolated aortic stenosis in the patient group aged 16 to 65.[2] In patients over the age of 65, aortic stenosis superimposed on a BAV occurs with a fre-

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Manuscript received August 21, 1989; revised manuscript received and accepted September 1, 1989.

TABLE I Hemodynamic Data

	Catheterization
Pressures (mm Hg)	
Right atrium (mean)	4
Right ventricle (ps/ed)	50/8
Pulmonary artery (ps/ed)	55/26
Pulmonary artery wedge (mean)	22
Left ventricle (ps/ed)	185/20
Aorta (ps/ed)	105/55
Aorta to left ventricle systolic gradient	80 (peak)
Aortic regurgitation	1+/4+
Aortic valve calcium	3+/4+
Cardiac index (liters/min/m^2)	2.0
Aortic valve area (cm^2)	0.4*

* Calculated using the Gorlin formula.
ps/ed = peak systole/end-diastole.

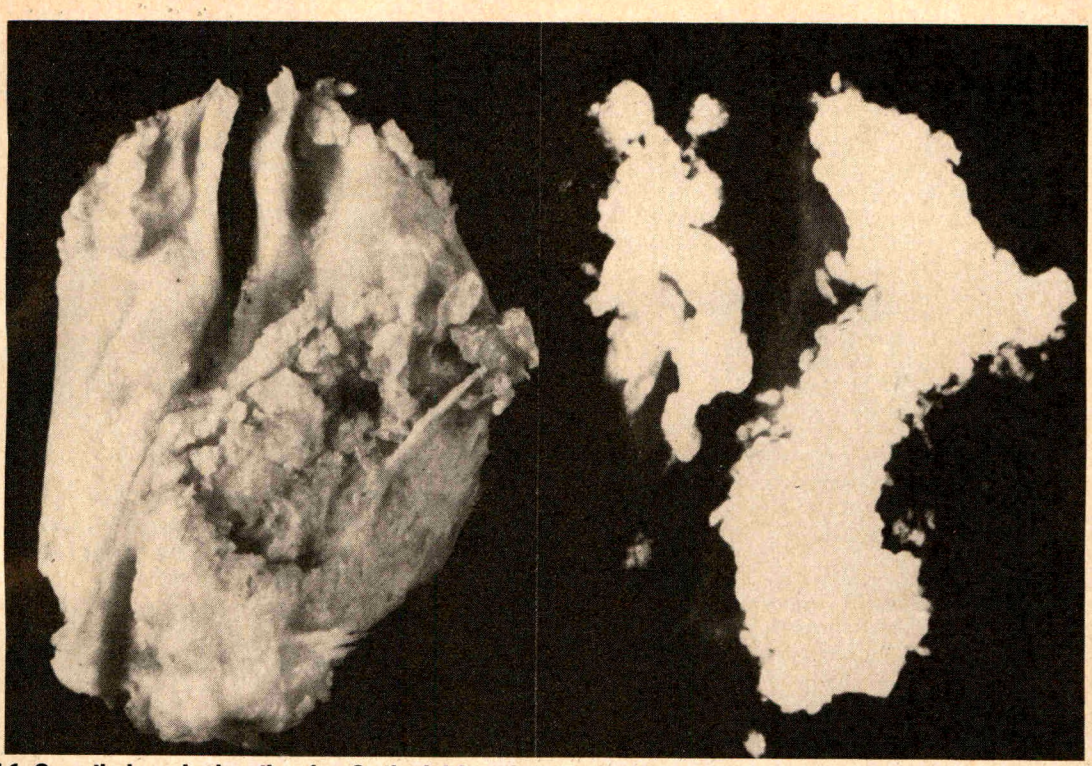


FIGURE 1. Operatively excised aortic valve. On the *left* is a photograph of the ventricular surface of the excised aortic valve. Both cusps were thickened, immobile and heavily calcified. On the *right* is a soft tissue roentgenogram demonstrating heavy calcific deposits in both cusps.

quency of approximately 10%. We recently encountered a 92-year-old man with severe aortic stenosis due to a congenitally BAV. To our knowledge, this is the oldest reported patient with severe stenosis involving a congenitally BAV.

The 92-year-old man, previously in good health, was referred for evaluation of recent onset congestive heart failure. His blood pressure was 130/70 mm Hg. The carotid upstrokes were delayed and the apical impulse was sustained and displaced laterally. An S_4 gallop was present. The S_2 was single. There was a harsh grade 3/6 precordial systolic murmur. The electrocardiogram demonstrated normal sinus rhythm and left ventricular hypertrophy. Two-dimensional transthoracic echocardiography demonstrated a heavily calcified and immobile aortic valve. Peak velocity across the valve was 5.0 m/s. Using the simplified Bernoulli equation ($P = 4V^2$), the estimated instantaneous peak gradient was 100 mm Hg. Mild aortic regurgitation was present. The Doppler-estimated aortic valve area was 0.4 cm^2 using the continuity equation. Transesophageal echocardiography revealed a BAV. Complete cardiac catheterization data are listed in Table I. The patient underwent valve replacement with a Carpentier-Edwards bioprosthesis. The valve was congenitally bicuspid (Figure 1).

One year postoperatively, the patient is asymptomatic.

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Disopyramide in Hypertrophic Cardiomyopathy

Both articles by Pollick[1,2] erroneously suggest a too prominent role of the outflow tract pressure gradient in the management of patients with hypertrophic obstructive cardiomyopathy. In both the invasive and noninvasive study disopyramide is advocated as an ideal drug for reduction of the left ventricular outflow tract obstruction as represented by a pressure gradient. Both studies strongly suggest that "de-obstruction" of the outflow tract by eliminating the pressure gradient invariably results in a beneficial effect for the heart and the patient. However, neither study yields convincing evidence that the reported beneficial effects can be ascribed only to the reduction of the pressure gradient.

First, after disopyramide, systolic emptying does not increase for cardiac output or heart rate; thus stroke volume remains unchanged (Table I, Figure 2A, page 1249; Table II, page 1250). The same stroke volume of 56 ml is now expelled in a shorter ejection time; however, it is at the expense of a significant reduction in ejection fraction as estimated from the ratio of the preejection period and ejection time in the hemodynamic study (Table II, page 1250).

Second, the small decrease in left ventricular end-diastolic pressure may only be appreciated as beneficial in conjunction with a simultaneously measured increase in end-diastolic volume. However, data from Table II (page 1253) indicate that the end-diastolic volume as calculated from the left ventricular end-diastolic dimension does not increase even despite a supposed reduction in mitral reflux.

Third, we[3,4] and others[5,6] did find a normal or low systolic wall stress as representative of afterload in hypertrophic cardiomyopathy (HC). Depending on the severity of the pressure gradient, peak systolic wall stress only differs in timing, not in magnitude. Thus we cannot support the suggestion that a reduction of the pressure gradient is followed by a further reduction of a normal ventricular afterload.

Fourth, the small but significant increase in exercise duration in the noninvasive study may be ascribed to a more uniform and coordinated pattern of relaxation due to the calcium antagonistic effect of disopyramide rather than to the reduction of the pressure gradient, an effect similar to that of verapamil. In this regard it would be interesting to investigate the effect of disopyramide in the nonobstructive form of HC. In conclusion, the results of both studies do not permit the focus on the pressure gradient as a prime determinant in left ventricular dysfunction and management of hypertrophic obstructive cardiomyopathy.

E. van der Wall, MD
Groningen, The Netherlands
15 February 1989

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REPLY: I thank van der Wall for his interest and comments. First, he remarks that there is a significant reduction in the ejection fraction, which he implies as being harmful although he does not say why. Most of these patients, however, have "supernormal" ejection fractions and disopyramide could be conceived as "normalizing" the ejection fraction.

Second, the interpretation of left ventricular compliance from left ventricular end-diastolic pressure alone is clearly somewhat limited. While the exact meaning of the disopyramide-induced decrease in left ventricular end-diastolic pressure is debatable, it is nevertheless presumably of benefit. In contrast, an increase in left ventricular end-diastolic pressure would have been considered deleterious.

Third, in his study of 19 patients[3] van der Wall clearly showed that 8 of 12 of the obstructive patients had an abnormal wall stress curve (type A), consisting of a definite increase in wall stress after obstruction. Three of 6 patients showed a change in the wall stress curve to a "nonobstructive" (type B) curve after verapamil. Thus I believe that his own data could well be interpreted as suggesting that a negative inotrope favorably alters wall stress via a reduction in the pressure gradient. By using disopyramide instead of verapamil, which appears to have a greater effect on the pressure gradient, perhaps all 6 patients would have developed a "nonobstructive" stress curve.

Fourth, his point is well taken that there may be other reasons that contribute to the increase in exercise duration such as a more uniform and coordinated left ventricular relaxation.

Charles Pollick, MB
Toronto, Canada
3 March 1989

Magnesium Sulfate Is the Treatment for Torsades de Pointes if the Right Dose Is Given

We were delighted to read about magnesium as a treatment of ventricular arrhythmias in the report of Roden[1] in the recent symposium on magnesium deficiency. In the section "Long QT-Related Arrhythmias," in the paragraph dealing with the effectiveness of magnesium as a treatment for torsades de pointes, we were surprised to find that we were misquoted by the investigator on a critical point addressing the dose of magnesium that should be used.

According to our published data,[2] magnesium sulfate is a very effective therapy for torsades de pointes. It was administered to 12 patients with this arrhythmia as a 2-g intravenous bolus within 1 to 2 minutes. In 9 patients the torsades de pointes was immediately abolished after the initial dose. Three other patients who did not respond completely to the first magnesium sulfate bolus received a second bolus of 2 g within 5 to 15 minutes after the first bolus. Most patients received additional magnesium sulfate infusions at rates of 3 to 20 mg/min for as long as 7 to 48 hours, until the QT interval was shortened to <0.50 second.

Torsades de pointes can be a fatal ventricular arrhythmia and intravenous magnesium is a very effective therapy for it, *if used in the right dose.* Administering a lower dose of magnesium over a longer period of time might not be as effective.

Shmuel Banai, MD
Claudio Schuger, MD
Jerusalem, Israel
4 May 1989

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2. Tzivoni D, Banai S, Schuger C, Benhorin J, Gottlieb S, Keren A, Stern S. Treatment of torsade-de-pointes with magnesium sulfate. *Circulation 1988;77:392–397.*

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A Brief Summary follows.

CONTRAINDICATIONS. 1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.

2. Preexisting gallbladder disease (See WARNINGS).

3. Hypersensitivity to gemfibrozil.

WARNINGS. 1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization (WHO), 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant, 29%, higher total mortality in the clofibrate-treated than in a comparable placebo-treated control group. The excess mortality was due to a 33% increase in noncardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

During the Helsinki Heart Study and in the 1½ year follow-up period since the trial was completed, mortality from any cause was 59 (2.9%) in the Lopid group and 55 (2.7%) in the placebo group. Mortality from any cause during the double-blind portion of the study was 44 deaths in the Lopid group and 43 in the placebo group. Because of the more limited size of the Helsinki Heart Study, this result is not statistically-significantly different from the 29% excess mortality seen in the clofibrate group in the separate WHO study. Noncoronary heart disease related mortality showed a 58% greater trend in the Lopid group (43 vs 27 patients in the placebo group, p=0.056).

In the Helsinki Heart Study, the incidence of total malignancies discovered during the trial and in the 1½ years since the trial was completed was 39 in the Lopid group and 29 in the placebo group (difference not statistically significant). This includes 5 basal cell carcinomas in the Lopid group and none in the placebo group (p=0.06; historical data predicted an expected 4.7 cases in the placebo group). GI malignancies and deaths from malignancies were not statistically different between Lopid and placebo subgroups. Follow-up of the Helsinki Heart Study participants will provide further information on cause-specific mortality and cancer morbidity.

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2. A gallstone prevalence substudy of 450 Helsinki Heart Study participants showed a trend toward a greater prevalence of gallstones during the study within the Lopid treatment group (7.5% vs 4.9% for the placebo group, a 55% excess for the gemfibrozil group). A trend toward a greater incidence of gallbladder surgery was observed for the Lopid group (17 vs 11 subjects, a 54% excess). This result did not differ statistically from the increased incidence of cholecystectomy observed in the WHO study in the group treated with clofibrate. Both clofibrate and gemfibrozil may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Lopid therapy should be discontinued if gallstones are found.

3. Since a reduction of mortality from coronary artery disease has not been demonstrated and because liver and interstitial cell testicular tumors were increased in rats, Lopid should be administered only to those patients described in the INDICATIONS AND USAGE section. If a significant serum lipid response is not obtained, Lopid should be discontinued.

4. Concomitant Anticoagulants—Caution should be exercised when anticoagulants are given in conjunction with Lopid. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

5. Concomitant therapy with Lopid and Mevacor® (lovastatin) has been associated with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure (See Drug Interactions). The use of fibrates alone, including Lopid, may occasionally be associated with myositis. Patients receiving Lopid and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myositis, including serum creatine kinase level determination. If myositis is suspected or diagnosed, Lopid therapy should be withdrawn.

6. Cataracts—Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of male rats treated with gemfibrozil at 10 times the human dose.

PRECAUTIONS. 1. **Initial Therapy**—Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal. Before instituting Lopid therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities.

2. **Continued Therapy**—Periodic determination of serum lipids should be obtained, and the drug withdrawn if lipid response is inadequate after 3 months of therapy.

3. **Drug Interactions**—(A) **Lovastatin:** Rhabdomyolysis has occurred with combined gemfibrozil and lovastatin therapy. It may be seen as early as 3 weeks after initiation of combined therapy or after several months. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. There is no assurance that periodic monitoring of creatine kinase will prevent the occurrence of severe myopathy and kidney damage.

(B) **Anticoagulants:** CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

4. **Carcinogenesis, Mutagenesis, Impairment of Fertility**—Long-term studies have been conducted in rats and mice at one and ten times the human dose. The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant (p=0.1). In high dose female rats, there was a significant increase in the combined incidence of benign, and malignant liver neoplasms. In male and female mice, there were no statistically significant differences

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from controls in the incidence of liver tumors, but the doses tested were lower than those shown to be carcinogenic with other fibrates.

Male rats had a dose-related and statistically significant increase of benign Leydig cell tumors at 1 and 10 times the human dose.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following Lopid administration to the male rat. An adequate study to test for peroxisome proliferation has not been done in humans but changes in peroxisome morphology have been observed. Peroxisome proliferation has been shown to occur in humans with either of two other drugs of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Administration of approximately three or ten times the human dose to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to the offspring.

5. **Pregnancy Category B**—Reproduction studies have been performed in the rat at doses 3 and 9 times the human dose, and in the rabbit at 2 and 6.7 times the human dose. These studies have revealed no evidence of impaired fertility in females or harm to the fetus due to Lopid. Minor fetotoxicity was manifested by reduced birth rates observed at the high dose levels. No significant malformations were found among almost 400 offspring from 36 litters of rats and 100 fetuses from 22 litters of rabbits.

There are no studies in pregnant women. In view of the fact that Lopid is tumorigenic in male and female rats, the use of Lopid in pregnancy should be reserved for those patients where the benefit clearly outweighs the possible risk to the patient or fetus.

6. **Nursing Mothers**—Because of the potential for tumorigenicity shown for gemfibrozil in rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

7. **Hematologic Changes**—Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of Lopid therapy. However, these levels stabilize during long-term administration. Rarely, severe anemia, leukopenia, thrombocytopenia, and bone marrow hypoplasia have been reported. Therefore, periodic blood counts are recommended during the first 12 months of Lopid administration.

8. **Liver Function**—Abnormal liver function tests have been observed occasionally during Lopid administration, including elevations of AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase. These are usually reversible when Lopid is discontinued. Therefore periodic liver function studies are recommended and Lopid therapy should be terminated if abnormalities persist.

9. **Use in Children**—Safety and efficacy in children have not been established.

ADVERSE REACTIONS. In the double-blind controlled phase of the Helsinki Heart Study, 2046 patients received Lopid for up to 5 years. In that study, the following adverse reactions were statistically more frequent in subjects in the Lopid group (placebo incidence in parentheses): gastrointestinal reactions, 34.2% (23.8%); dyspepsia, 19.6% (11.9%); abdominal pain, 9.8% (5.6%); acute appendicitis (histologically confirmed in most cases where data are available), 1.2% (0.6%); atrial fibrillation, 0.7% (0.1%).

Adverse events reported by more than 1% of subjects, but without a significant difference between groups (placebo incidence in parentheses) were: diarrhea, 7.2% (6.5%); fatigue, 3.8% (3.5%); nausea/vomiting, 2.5% (2.1%); eczema, 1.9% (1.2%); rash, 1.7% (1.3%); vertigo, 1.5% (1.3%); constipation, 1.4% (1.3%); headache, 1.2% (1.1%).

Gallbladder surgery was performed in 0.9% of Lopid and 0.5% of placebo subjects, a 64% excess, which is not statistically different from the excess of gallbladder surgery observed in the clofibrate compared to the placebo group of the WHO study.

Nervous system and special senses adverse reactions were more common in the Lopid group. These included hypesthesia, paresthesias, and taste perversion. Other adverse reactions that were more common among Lopid treatment group subjects but where a causal relationship was not established include cataracts, peripheral vascular disease, and intracerebral hemorrhage.

From other studies it seems probable that Lopid is causally related to the occurrence of **musculoskeletal symptoms** (See WARNINGS), and to **abnormal liver function tests** and **hematologic changes** (See PRECAUTIONS).

Reports of viral and bacterial infections (common cold, cough, urinary tract infections) were more common in gemfibrozil-treated patients in other controlled clinical trials of 805 patients.

Additional adverse reactions that have been reported for gemfibrozil are listed below by system. These are categorized according to whether a causal relationship to treatment with Lopid is probable or not established:

CAUSAL RELATIONSHIP PROBABLE: *Gastrointestinal:* cholestatic jaundice; *Central Nervous System:* dizziness, somnolence, paresthesia, peripheral neuritis, decreased libido, depression, headache; *Eye:* blurred vision; *Genitourinary:* impotence; *Musculoskeletal:* myopathy, myasthenia, myalgia, painful extremities, arthralgia, synovitis, rhabdomyolysis (see WARNINGS and Drug Interactions under PRECAUTIONS); *Clinical Laboratory:* increased creatine phosphokinase, increased bilirubin, increased liver transaminases (AST [SGOT], ALT [SGPT]), increased alkaline phosphatase; *Hematopoietic:* anemia, leukopenia, bone marrow hypoplasia, eosinophilia; *Immunologic:* angioedema, laryngeal edema, urticaria; *Integumentary:* exfoliative dermatitis, rash, dermatitis, pruritus.

CAUSAL RELATIONSHIP NOT ESTABLISHED: *General:* weight loss; *Cardiac:* extrasystoles; *Gastrointestinal:* pancreatitis, hepatoma, colitis; *Central Nervous System:* confusion, convulsions, syncope; *Eye:* retinal edema; *Genitourinary:* decreased male fertility; *Clinical Laboratory:* positive antinuclear antibody; *Hematopoietic:* thrombocytopenia; *Immunologic:* anaphylaxis, Lupus-like syndrome, vasculitis; *Integumentary:* alopecia.

DOSAGE AND ADMINISTRATION. The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal.

MANAGEMENT OF OVERDOSE. While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

References: 1. Frick MH, Elo O, Haapa K, et al: Helsinki Heart Study: Primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia. *N Engl J Med* 1987;317:1237-1245. 2. Manninen V, Elo O, Frick MH, et al: Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study. *JAMA* 1988; 260:641-651. 3. Nikkila EA: Familial lipoprotein lipase deficiency and related disorders of chylomicron metabolism. In Stanbury J. B. et al. (eds.): *The Metabolic Basis of Inherited Disease,* 5th ed., McGraw-Hill, 1983, Chap. 30, pp. 622-642.

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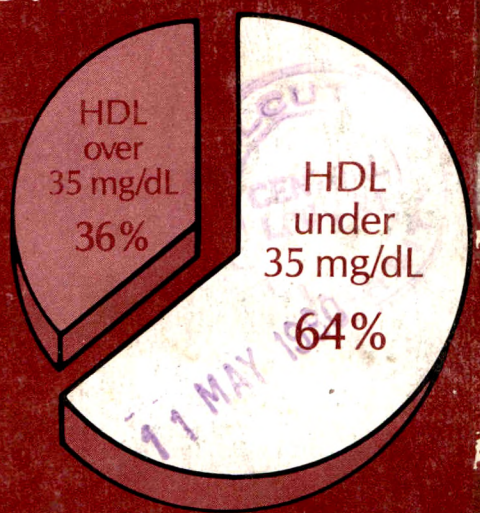
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RAISES HDL...DRAMATICALLY REDUCES HEART ATTACK

LOPID is indicated for reducing the risk of coronary heart disease (CHD) in Type IIb patients with low HDL, in addition to elevated LDL and triglycerides, and who have had an inadequate response to weight loss, diet, exercise, and other pharmacologic agents such as bile acid sequestrants and nicotinic acid.

*Defined as a combination of definite coronary death and/or definite myocardial infarction.

References: 1. Goldstein JL, Hazzard WR, Schrott HG, Bierman EL, Motulsky AG. Hyperlipidemia in coronary heart disease. I. Lipid levels in 500 survivors of myocardial infarction. *J Clin Invest.* 1973;52:1533-1543. **2.** Assmann G, Schulte H. *PROCAM-Trial: Prospective Cardiovascular Münster Trial.* Zürich: Panscientia Verlag; 1986:8-9. **3.** Data on file, Medical Affairs Dept, Parke-Davis.

Please see adjacent page of this advertisement for warnings, contraindications, and brief summary of prescribing information.

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